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Entecavir for the treatment of chronic hepatitis B

Produced by Southampton Health Technology Assessments Centre (SHTAC)

Authors Jonathan Shepherd, Elena Gospodarevskaya, Geoff Frampton, Keith Cooper

Correspondence to Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute for Health Research and Development
University of Southampton
Mailpoint 728, Boldrewood
Southampton SO16 7PX, UK

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[redacted]

Conflicts of Interest:

None

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LIST OF ABBREVIATIONS

ALT	Alanine aminotransferase
AASLD	American Association for the Study of Liver Diseases
bDNA	Branched-chain deoxyribonucleic acid
BMS	Bristol-Myers Squibb
BNF	British National Formulary
CAS	Chemical Abstracts Service (reference number)
CCRCT	Cochrane Central Register of Controlled Trials
CEA	Cost effectiveness analysis
CEAC	Cost Effectiveness Acceptability Curve
CDSR	Cochrane Database of Systematic Reviews
CHB	Chronic hepatitis B
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
DARE	Database of Reviews of Effectiveness
EASL	European Association for the Study of Liver Diseases
ERG	Evidence Review Group
GDP	Gross Domestic Product
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of LIfe
ITT	Intention to treat
LLOQ	Lower limit of quantification
MEIP	Medline in Progress (MEIP)
MEq/mL	Milliequivalents per millilitre
mg	Milligram
MTC	Mixed Treatment Comparison
NA	Nucleotide / nucleoside analogue
NC=F	Analysis method in which non-conformers are analysed as treatment failures
NC=M	Analysis method in which non-conformers are analysed as missing data
NMA	Network meta-analysis
NRR	National Research Register
Peg IFN	Pegylated interferon alpha 2a
PDF	Portable document format
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
qd	Once daily
RCT	Randomised Controlled Trial
QALY	Quality Adjusted Life Year
SD	Standard Deviation
SE	Standard Error
SG	Standard Gamble

SMC	Scottish Medicines Consortium
SMPC	Summary of product characteristics
TRIP	Turning Research into Practice
TTO	Time trade off
ULN	Upper limit of normal
YMDD	Tyrosine methionine aspartate aspartate motif in the catalytic domain of the viral polymerase/reverse transcriptase

SUMMARY

Scope of the submission

The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE), the licensed indication, and is appropriate to the National Health Service (NHS).

- The population described is adults with chronic hepatitis B (CHB) infection with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. Patient sub-groups include those with HBeAg positive and HBeAg negative CHB; and those who are treatment (nucleoside analogue) naïve or refractory to lamivudine (e.g. those with persistent viraemia and/or genotypical resistance). Patients with co-infections were excluded in accordance with the scope.
- The intervention is entecavir alone in the treatment of CHB.
- Comparators include nucleoside analogues: lamivudine and telbivudine; nucleotide analogue: adefovir dipivoxil, and immune modifiers: interferon alpha 2a and 2b, and pegylated interferon alpha 2a.
- Outcomes include: HBeAg/HBsAg seroconversion rate, virological response (HBV DNA); histological improvement (liver inflammation and fibrosis); biochemical response (e.g. ALT levels); development of viral resistance; and adverse events. Outcomes included in the scope and decision problem but not reported in the submission include time to treatment failure; survival (unless within the context of adverse events) and health related quality of life.

Summary of submitted clinical effectiveness evidence

The manufacturer's systematic review includes five randomised controlled trials (RCTs) all of which compared entecavir with lamivudine:

- Three of the trials were conducted in nucleoside-naïve patients (one in HBeAg positive patients, one in HBeAg negative patients, and one in a mixed HBeAg positive and negative status group).

- The other two were conducted in lamivudine-refractory patients (one in HBeAg positive patients, the other in a mixed HBeAg positive and negative status group).
- Outcome data are reported for up to one year of treatment, and for a sub-set of patients who did not achieve a complete response and who continued treatment in year two. Cumulative proportions of all patients ever attaining treatment response up to two years are also presented. Some of the patients from the RCTs have entered long-term observational extension studies, with treatment continuing up to five years. However, fully published data are not yet available.

The results of the five RCTs showed that:

- After one year of treatment entecavir was statistically superior to lamivudine in terms of the proportion of patients achieving HBV DNA suppression; ALT normalisation; and histological improvement. There was no statistically significant difference between the treatments in the proportion of patients achieving HBeAg seroconversion (HBeAg positive patients only, by definition).
- [redacted]Most of the entecavir-treated patients did not have any detectable resistance-associated substitutions at one year of treatment.
- The proportions of patients with any adverse events or serious adverse events were similar for entecavir and lamivudine. The proportion of patients who withdrew during the first year due to adverse events was similar for entecavir and lamivudine except in one trial where significantly more lamivudine patients withdrew. The number of deaths during treatment was low (<1% in all cases).

The manufacturer also constructed a mixed treatment comparison (MTC) model to compare entecavir with the comparator drugs, in nucleoside-naïve patients. An MTC was not considered possible in lamivudine-refractory patients due to lack of evidence.

- The results of the MTC generally accord with the results of the RCTs, in that entecavir was superior to lamivudine across outcomes, with the exception of HBeAg seroconversion.
- The MTC suggests that entecavir is either significantly better or equivalent to the other comparators, depending on the outcome measure and the time-point.

Summary of submitted cost effectiveness evidence

- The manufacturer's economic evaluation comprises a systematic review of economic evaluations of CHB treatments, and a cost-utility analysis based on a *de novo* economic model.
- Two Markov state-transition models were constructed, one in HBeAg positive patients and one in HBeAg negative patients. The models estimate progression to 14 health states (15 in the HBeAg negative model) representative of progressive CHB related liver disease (e.g. compensated and decompensated cirrhosis; hepatocellular carcinoma). The models have a lifetime horizon and a cycle length of one year.
- In HBeAg positive and negative nucleoside naïve patients, the models compare entecavir with lamivudine, pegylated interferon alpha 2a, and telbivudine. Treatment lasts for two years in HBeAg positive patients, and five years in HBeAg negative patients (with the exception of pegylated interferon alpha 2a which is given for only one year). In HBeAg positive patients who are refractory to lamivudine, entecavir is compared to adefovir added to lamivudine for two years. Response to treatment is defined by HBeAg seroconversion and undetectable HBV DNA.
- In HBeAg positive patients the base case incremental cost-effectiveness ratio (ICER) for entecavir compared to lamivudine was £14,329 per Quality Adjusted Life Year (QALY). Compared to pegylated interferon alpha 2a, the ICER was £8,403 per QALY. Entecavir was associated with the same number of QALYs as telbivudine but at a slightly higher total cost and was therefore dominated. In HBeAg negative patients the base case ICERs were £13,208, £7,511 and £6,907 per QALY, in comparison to lamivudine, pegylated interferon alpha 2a and telbivudine, respectively. In HBeAg positive lamivudine-refractory patients entecavir dominated adefovir added to lamivudine.
- One-way deterministic sensitivity analysis for entecavir compared to lamivudine on all key input parameters, and performed for nucleoside naïve patients, showed that the results were most sensitive to baseline transition probabilities from CHB to (a) seroconversion (spontaneous seroconversion), (b) active cirrhosis, from active cirrhosis to decompensated cirrhosis, baseline cirrhosis risk and treatment effects. ICERs generally remained under £30,000 per QALY.
- Results of the probabilistic sensitivity analysis in nucleoside naïve HBeAg positive patients show that the probability of the ICER for entecavir being below £20,000 per QALY was 57% compared to lamivudine, 82% compared to pegylated interferon alpha 2a, and 45%

compared to telbivudine. In nucleoside naïve HBeAg negative patients the probabilities were 90%, 100% and 96%, respectively.

- The manufacturer included a lifetime treatment scenario in HBeAg negative patients, and the ERG included a scenario of up to 20 years treatment for HBeAg positive patients. The ICERs increased as a consequence, particularly in the latter.

Commentary on the robustness of submitted evidence

Strengths

- The MS conducted a systematic search for clinical- and cost-effectiveness studies of entecavir. It appears unlikely that the searches missed any additional trials that would have met the inclusion criteria.
- The five entecavir RCTs identified were of generally good methodological quality, and measured a range of outcomes that are appropriate and clinically relevant, although health related quality of life was not reported.
- Overall, the MS presents an unbiased estimate of the efficacy of entecavir versus lamivudine, based on the results of the five RCTs.
- Overall, the manufacturer's economic evaluation accords with the decision problem and the NICE reference case. The approach to modelling was generally considered reasonable and the model was judged to be internally and externally consistent, subject to some uncertainties (see below).
- Disease progression pathways assumed in the economic models are generally consistent with the natural history of CHB, although there were some concerns about some of the structural assumptions (see below).

Weaknesses

- The mixed treatment comparison model (MTC) suffers from certain limitations in conduct and reporting, including: small numbers of studies / single studies in some networks; no assessment or discussion of heterogeneity; and no reporting of criteria for judging statistical significance or equivalence.

Areas of uncertainty

- Given the concerns about the conduct and reporting of the MTC the ERG consider its results to be uncertain. This limits any conclusions that can be drawn regarding the comparative efficacy of entecavir to telbivudine, and to pegylated interferon alpha 2a in nucleoside-naïve patients (NB. notwithstanding the head-to-head RCT evidence comparing entecavir with lamivudine).
- There is relatively limited clinical and cost-effectiveness evidence for entecavir in lamivudine-refractory patients. Head-to-head RCT evidence is available for entecavir versus on-going lamivudine, but only in HBeAg positive patients. Smaller RCTs have been published comparing switching to adefovir versus adding adefovir to on-going lamivudine, but these have not been compared in a statistical indirect comparison to entecavir. The manufacturer only present cost-effectiveness estimates for HBeAg positive, not HBeAg negative, lamivudine-refractory patients.
- Structural assumptions in both the HBeAg positive and HBeAg negative disease models preclude the patients with response from directly entering the active/compensated cirrhosis health state. The rationale for this assumption was not clear and it is not possible to estimate the impact of these structural assumptions.
- Treatment of CHB in many patients will be longer than the two and five years assumed in the HBeAg positive and HBeAg negative disease models, respectively. However, there a paucity of published clinical effectiveness data from RCTs beyond the second year of treatment (NB. long-term observational studies (up to five years) are in progress). Increasing the treatment duration in scenario analysis results in higher ICERs.
- No data are presented in the submission of the efficacy and safety of entecavir in combination with other licensed agents.
- Contrary to the assumptions in the manufacturer's economic evaluation, a certain proportion of CHB patients will first present with compensated cirrhosis. Moreover, it is unlikely that the treatment is terminated once the patients progress to the active cirrhosis stage of disease. Changing these assumptions to reflect a more realistic scenario increased the ICER for entecavir compared to lamivudine.

Key issues

The validity and reliability of results of the cost-effectiveness analysis are likely to be affected by the following:

- The uncertain effect of the modelling assumption of patients with response transitioning exclusively to the inactive cirrhosis state;

- The assumed duration of nucleoside treatment in the base case analyses of two and five years in HBeAg positive and HBeAg negative patients respectively does not reflect clinical practice.
- The exclusion of patients who progress to the active cirrhosis state from receiving treatment for CHB;
- The assumption that all the patients are first presented at the pre-cirrhotic state of disease;

1 Introduction to ERG Report

This report is a critique of the manufacturer's submission (MS) to NICE from Bristol Myers Squibb on the clinical effectiveness and cost effectiveness of entecavir for chronic hepatitis B (CHB). It identifies the strengths and weakness of the MS. Clinical experts were consulted to advise the ERG and to help inform this review.

Clarification on some aspects of the MS was requested from the manufacturer by the ERG via NICE on 12th December 2008. A response from the manufacturer via NICE was received by the ERG on 24th December 2008 and this has been included as an Addendum in this report (Appendix 1). Annotations referring to the Addendum occur throughout the ERG report where applicable.

The ERG noted that labelling of tables and sections in the MS is inconsistent:

- Tables on MS pages 32-34, 44-46, 47-51, 57-59, 60-62, 63-65, 94, 95 and 96 have no number or caption but are immediately preceded by section numbers which help to identify them. Where necessary these tables are cited in the ERG report by their section and page numbers.
- Tables on MS pages 67, 68, 71, 72, 74, 75, 77, 78, 80, 90 have no numbers or captions and are not preceded by section headings. Where necessary these tables are cited in the ERG report by their page numbers.
- The order of tables in relation to sections is somewhat confusing, with Tables 5.1 to 5.4 (pages 36-41) preceding Tables in section 5.3 (pages 44-65). This makes some tables less easy to find in the MS but does not affect cross-referencing or interpretation of data.
- Table 5.3 (MS page 41) is incorrectly labelled Table 5.1.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The manufacturer has provided a reasonably comprehensive overview of the condition. A distinction between HBeAg positive and HBeAg negative forms of the disease is provided, although differences in disease progression between the two is not discussed. The specific phases of the disease are not mentioned (e.g. the immune tolerant phase; the

immunoactive/immune clearance phase; the inactive carrier/immune control phase and the immune escape phase). Treatment is indicated in the immunoactive/immune clearance phase and if successful leads to inactive carrier status, although reactivation can occur at the immune escape phase[1]. It would have been helpful to mention these phases as it puts the rest of the submission, particularly the economic model, into context.

The manufacturer reports that there are around 180,000 people infected with CHB in the UK , based on 2004 prevalence figures reported by the British Liver Trust. If only England and Wales are considered then the prevalence is around 156,000. The Hepatitis B Foundation recently estimated that the prevalence of CHB in the UK has increased to 325,000 (not mentioned in the MS) and is thought likely to increase further as a consequence of increasing rates of immigration of people from countries with a high CHB prevalence[2].

2.2 Critique of manufacturer's overview of current service provision

The manufacturer provides a clear and generally accurate overview of current service provision. Recently published clinical guidelines are described, such as those produced by the American Association for the Study of the Liver. It is noted that European guidelines were published in 2003, but are now out of date. There are currently no UK clinical guidelines, although NICE's 2006 guidance on the use of pegylated interferon alpha and adefovir dipivoxil is described. No other UK relevant guidelines are known to the ERG.

It is noted that, based on market research, only a small selected group of patients in the UK begin treatment with an interferon (<10%, of which >85% use pegylated interferon alpha), of which around a third will undergo HBeAg seroconversion and enter the inactive carrier stage of infection. It is suggested that the role of interferon is less clear in HBeAg negative patients who, by definition, cannot seroconvert. In such patients initiation of therapy with a nucleoside analogue is the most likely option. Expert clinical opinion sought by the ERG confirms this, with a circumscribed course of interferon primarily aiming to induce seroconversion via an immuno-modulatory response. Nucleoside analogues, in contrast, aim to induce viral suppression and are therefore more suited to longer-term therapy in patients in whom HBeAg seroconversion is less likely/not possible. Interferon is therefore used as a first line therapy primarily for HBeAg positive CHB patients with compensated liver disease, although some HBeAg negative patients will also receive it.

The manufacturer states that lamivudine is the most commonly used treatment in nucleoside-naïve CHB patients in the UK, with the addition of adefovir as rescue therapy upon emergence of viral resistance. This is based on market research data (cited as data on file). It suggests that only a minimal amount of evidence exists to support the use of adefovir as a rescue treatment in lamivudine resistance. This appears a reasonable assertion as the pivotal trials of adefovir were conducted in largely nucleoside-naïve patients.[3,4] However, the manufacturer could have cited the two RCTs evaluating adefovir rescue treatment [5,6] that were included in the assessment that underpinned NICE's guidance[7]. These trials are not cited in relation to the manufacturer's assertion, although they are reported in a later section for purposes of an indirect comparison in lamivudine-refractory patients (section 5.6.5 of the MS).

The manufacturer suggests that there is a degree of uncertainty regarding current best practice particularly in relation to choice of drug, and viral resistance (MS, page 30). It is noted that there is a lack of consensus around treatment pathways, and clinical experts consulted by the ERG agree with this to some extent. Aside from the 12 specialist centres around the UK, the majority of patients will be treated in District General Hospitals by gastroenterologists who have limited training in Hepatology.

A comparison of the international clinical guidelines is presented in a table (MS section 4.6). In all guidelines presented entecavir is one of the recommended first line treatments.

The MS suggests that there is no consensus around the optimal treatment duration in HBeAg negative patients (p. 24). Clinical experts consulted by the ERG reported that, in practice, the majority of these patients will receive life-long treatment. Thomas (2007), in a review of international clinical guidelines on the management of CHB, suggests that the effectiveness of treatment discontinuation should be subjected to further evaluation[1].

2.3 Critique of manufacturer's definition of decision problem

2.3.1 Population

The population described in the decision problem is adults with CHB infection with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine

aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis. This matches the scope for the appraisal, the licensed indication, and is appropriate for the NHS. However, the scope and the decision problem do not include patients with advanced (decompensated) liver disease, including pre and post liver transplant patients. Therefore, the submission (and the appraisal) will not be relevant for this patient group. The scope and the decision problem also do not include patients who are co-infected with human immuno-deficiency virus (HIV) or hepatitis C (HCV) or D (HDV). The decision problem distinguishes between sub-groups of patients, in accordance with the scope, namely HBeAg positive and negative patients, and treatment naïve patients and treatment (nucleoside analogue) resistant patients.

2.3.2 Intervention

The intervention described in the decision problem is entecavir alone in the treatment of CHB. This reflects the licensed indication and is appropriate for the NHS. However, the scope specified that the intervention could be entecavir alone or in combination with other therapies. No mention is made of combination therapies in the decision problem. It is not clear whether the absence of mention of combination therapy in the licensed indication prohibits such use. It is also of note that none of the randomised controlled trials (RCTs) of entecavir identified by the manufacturer has evaluated its use in combination with other drugs.

The MS states that the optimal duration of treatment is unknown and cites the summary of product characteristics (SPC)[8] which provides guidance on when to discontinue treatment. In HBeAg positive patients treatment should be continued until HBeAg seroconversion or until HBsAg seroconversion, or if there is evidence of loss of efficacy. In HBeAg negative patients treatment should be continued until HBs seroconversion or if there is loss of efficacy. Patients on long-term therapy (> 2 years) should be reassessed regularly to determine whether that particular treatment is still appropriate.

Expert clinical opinion suggests that entecavir is currently used in some parts of England and Wales, although generally not as a first line treatment. Clinical opinion also suggests that for those who have failed to respond to, or who have relapsed, following interferon or pegylated interferon alpha, it would be advantageous to proceed directly to a combination of entecavir and another nucleoside / nucleotide analogue. It is thought that this would lessen the risk of cross-

resistance, a problem associated with the sequential use of nucleoside / nucleotide analogue monotherapies. This is also a problem that has been experienced in the HIV/AIDS and tuberculosis fields, where combination therapies are now commonplace.

2.3.3 Comparators

The comparators listed in the decision problem reflect those in the scope of the appraisal and are all appropriate to the NHS. These include pegylated and non-pegylated interferon alpha-2a, lamivudine, telbivudine, and adefovir dipivoxil. The MS presents head-to-head RCT data for entecavir compared with lamivudine, and indirect evidence via network meta-analysis for entecavir compared with telbivudine and pegylated interferon alpha-2a.

2.3.4 Outcomes

The comparators listed in the decision problem reflect those in the scope of the appraisal and are all appropriate to current clinical practice. These include viral response (HBV DNA); HBeAg loss and seroconversion (only in patients who are HBeAg positive, by definition); HBsAg loss and seroconversion; biochemical response (ALT - alanine amino transferase); development of viral resistance; histological improvement; health related quality of life (HRQoL); adverse events and survival. There do not appear to be any other clinically meaningful outcomes that have not been included.

Although not generally a primary outcome in the pivotal RCTs presented by the MS (see Section 3.1.4), the MS provides a rationale for why viral suppression should be considered as the key marker of treatment effect in their background section on CHB (MS section 4.5.1, page 28). Results of a large population based cohort study in Taiwan (the REVEAL study[9]) are cited as supporting the association between baseline viral load and the development of cirrhosis, hepatocellular carcinoma (HCC) and mortality. It is asserted that there are uncertainties around the appropriateness of other markers of treatment effect, namely ALT, histological improvement and HBeAg seroconversion. Expert clinical opinion agrees that viral suppression is a clinically meaningful treatment outcome, particularly in patients in whom HBeAg seroconversion is unlikely to occur (e.g. HBeAg positive patients who have not seroconverted or who have relapsed following earlier treatment, such as interferon alpha or pegylated interferon alpha), or in whom it is not applicable (e.g. HBeAg negative patients).

3 CLINICAL EFFECTIVENESS

3.1 Critique of manufacturer's approach

3.1.1 Description of manufacturer's search strategy

The manufacturer has provided a reasonably detailed description of its search strategies. However the ERG had to request clarification from the manufacturer on certain details, as outlined below.

3.1.1.1 Clinical effectiveness searches

The search process described was used to inform both the assessment of clinical effectiveness (section 5.1 of the MS) and the mixed treatment comparison (MTC) (section 5.6 of the MS).

The manufacturer has replicated the search strategies used by SHTAC in the previous assessment report on adefovir and pegylated interferon alpha 2a[7] which underpinned NICE's existing guidance (NICE Technology Appraisal 96). The manufacturer states that the full range of databases used by SHTAC were not searched for the submission due to difficulties in access. The minimum database search criteria specified by NICE were searched by the manufacturer (i.e. Medline, Embase, Medline in Progress (MEIP) and Cochrane). In addition, two of the Centre for Reviews and Dissemination (CRD) databases were also searched (DARE; HTA database). The host system used for the electronic bibliographic searching was not reported in the submission. The ERG requested clarification and the manufacturer reported that Dialog Datastar was used to search Embase, and that Ovid and Dialog Datastar had been used to search Medline (see Appendix 1, A4 and A5).

The SHTAC strategy was extended by the manufacturer to incorporate entecavir, telbivudine, and lamivudine. The searches were limited to articles published in the English language. No time limits were applied to the clinical effectiveness searches, but the ERG requested clarification about the search dates of the various electronic bibliographic databases, as these vary according to which host system is used. The manufacturer responded with the information

for each database (see Appendix 1, page 1). Each database was searched from its inception, up to approximately 21st September 2007.

The search strategy, as adapted for each bibliographic database, was not presented in the submission. However, the strategy for Medline, Embase and the Cochrane Library was supplied on request to the ERG (see Appendix 1, pages 10 to 13). The strategy contains a mixture of free text and index terms, although for the Embase search it is not explicit whether index terms were used. It is not clear from the search example given by the manufacturer if all the component databases of the Cochrane Library were searched or if the Cochrane Database of Systematic Reviews (CDSR) alone was used. The ERG noticed what appeared to be a few errors with the syntax used in the strategy and requested clarification from the manufacturer. The manufacturer confirmed that these were typographical errors in the submission, rather than errors in the strategies themselves (see Appendix 1, pages 2 and 3). The strategies appear to be comprehensive although only the generic names of the drugs were included in the strategy, rather than including trade names and CAS registry numbers or applying field tags to search for these. It is not considered, however, that using these would have produced any additional references.

The ERG also enquired whether the number of hits generated from each database could be supplied. The manufacturer reported that this information had not been saved by the agency who conducted the searching. Without this information it is not possible to reproduce the search strategies and compare search results.

The manufacturer also ran a 'simple search strategy' specifically to identify articles relating to entecavir. This was a bibliographic reference chasing exercise to check for any missed trials. It is stated that this strategy was also run for telbivudine (MS Appendix 8.3.1, page 1), although terms for this drug are not presented in the actual strategy itself (MS Appendix 8.3.1, page 18). There is no explanation of why the other comparator drugs were not subjected to the simple search approach. This is particularly important given that the other drugs were included in the MTC.

In terms of on-going trials the manufacturer reports searching clinicaltrials.gov (http://clinicaltrials.gov) and Current Controlled Trials (www.controlled-trials.com), as well as internal company databases. The National Research Register (NRR) is not reported as having

been searched, although this is not a NICE pre-requisite (NB. At the end of 2007 the NRR has been decommissioned and is now available as an archive only). Conference proceedings have not been reported as individually searched, although the Cochrane Central Register of Controlled Trials (CCRCT) has been searched and this does include hand-searched conference proceedings.

In summary, the search process for clinical effectiveness studies reported by the manufacturer is generally comprehensive, with key databases searched using a combination of free-text and index terms. The search strategy is not, however, fully reproducible due to limitations in reporting.

3.1.1.2 Cost effectiveness searches

The cost-effectiveness searches have satisfied most of the minimum database criteria set by NICE (namely, Medline, Embase, and MEIP). The manufacturer has exceeded the criteria by searching internal company databases, The Cochrane Library, the HTA databases, the TRIP database (Turning Research into Practice), and websites of organisations including NICE, The Scottish Medicines Consortium (SMC), The European Association for the Study of Liver Diseases (EASL), The American Association for the Study of Liver Diseases (AASLD), as well as a Google internet search. It is not explicitly stated whether the NHS Economic Evaluation database (NHS EED) was searched, but it is assumed it was accessed via the CRD databases which was were mentioned by the manufacturer as having been searched. It is not stated whether the Health Economic Evaluation Database (HEED), one of NICE's database criteria, was searched.

The date of the searches is recorded as "during September 5th and October 10th 2007".(MS page 101). The host system used for Embase and Medline is reported as www.embase.com. It is stated that no time limits were applied, so presumably all databases were searched back to their inception.

It is reported that all search terms were mapped to EMTREE terms and exploded, as well as included as free-text terms (MS, section 8.5.4). However, the strategy is not reproducible as the mapped terms are not recorded. It would have been preferable to record the exact search

strategy that included the free text terms and subject headings, so that it could be reproduced, or at least have clearly defined which terms were free text and which were index terms.

The search strategy is not entirely transparent and therefore not easily reproducible because the list of free text terms is given, but they have not necessarily recorded the mapped index terms (MS section 8.5.4 "All search terms were mapped to EMTREE terms and exploded as well as included in a free text term"). The range of free-text terms looks sensible but there is no overt truncation of free text terms, although it is thought that the Datastar Dialog platform can be programmed to identify plurals and variations of endings of words. There is no indication in the search strategy as to which fields have been searched (title, abstract, subject headings etc.). However, it does say that the mapped headings have been exploded.

3.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

Three different sets of inclusion criteria are presented in the MS, all of which were applied to the same set of search results.

- The first set is for the clinical effectiveness systematic review of entecavir studies presented in section 5.2.2 of the MS. This is the focus of the clinical effectiveness evidence for entecavir in the submission.
- The second set was for studies screened for possible inclusion in the MTC, and is presented in Appendix 8.4.
- The third set relates to a 'systematic review of licensed therapies for chronic hepatitis B', which incorporates adefovir, pegylated interferon alpha 2a, lamivudine, telbivudine and entecavir, presented in Appendix 8.3 of the MS.

Although these sets of criteria are generally similar there are some differences, and these are highlighted below.

Inclusion criteria for systematic review of entecavir (MS section 5.2.2)

The criteria are appropriate to the decision problem and the licensed indication. Trials were only included if one of the arms evaluated entecavir as a single agent. As mentioned earlier in section 2.3.2, the scope of the appraisal also permitted entecavir in combination with other

agents. It is not clear whether any trials of entecavir combination therapy have been conducted and published. Eligible comparators were lamivudine, telbivudine, and pegylated interferon alpha 2a in nucleoside-naïve patients, and the combination of adefovir and lamivudine in patients who were resistant to lamivudine. It is presumed that interferon alpha is not included as this drug has now been superseded by pegylated interferon alpha.

Note that the scope for the appraisal does not specify which patient sub-group the comparators have to be have been evaluated in (i.e. nucleoside-naïve or resistant to lamivudine). Consequently adefovir, in theory, could be the comparator in the treatment of nucleoside-naïve patients, despite current NICE guidance which specifies that it should not normally be given before treatment with lamivudine. However, the manufacturer's inclusion criteria accord with the guidance, in that trials in which adefovir is a comparator cannot be included unless it has been added to lamivudine in patients who are lamivudine resistant. As will be commented upon later, at least one RCT of adefovir in nucleoside-naïve patients appears to have been excluded on this basis (although it was included in the MTC in order to complete the data network - see section 3.1.2.1). Although placebo or standard care/no treatment trials were eligible they were to be excluded if active comparator trials were identified (NB. All five trials that were included compared entecavir with lamivudine – see section 3.3.1).

Eligible patients were adults with compensated liver disease and active CHB, either HBeAg positive or negative, and either nucleoside-naïve or lamivudine-refractory. Studies of patients with decompensated CHB liver disease were excluded, as were those which evaluated treatment of post-transplant patients, in accordance with the licensed indication. Studies of co-infected patients (e.g. with HIV) were also ineligible, in accordance with the scope and decision problem. Studies less than 48 weeks of duration were excluded, as it was considered that shorter studies would not capture end-points such as HBeAg seroconversion. This criterion was not mentioned in the scope or decision problem (although note that the QUOROM flowchart on page 42 of the MS shows that two of the entecavir studies screened were excluded on the basis of inadequate duration. From examination of the list of excluded studies in MS Appendix 8.3 it appears one was a 28 day study, whilst the other treated patients for 24 weeks).

Only fully published RCTs were eligible (see section 3.1.2.1), however, observational extension studies were permitted (these are reported in a separate section on 'Non-RCT evidence', MS page 92). All other observational studies were excluded. Studies published in abstract form

were excluded, and unpublished studies conducted by the manufacturer were only included where a clinical study report was available. Reviews were only analysed for bibliographic checking. Non-English language articles were excluded.

It is not stated whether screening was conducted independently by more than one person. However, independent screening was conducted for the systematic review of licensed therapies (see below, and MS Appendix 8.3, page 1) it is therefore presumed that a similar approach was used here.

Inclusion criteria for mixed treatment comparison (MTC) (MS section 5.5)

The MTC is presented in MS section 5.5, with further detail of the inclusion/exclusion criteria provided in MS Appendix 8.4.

- The relevant interventions were entecavir (0.5mg), lamivudine (100mg), pegylated interferon alpha 2a (180mg), and telbivudine (600mg). Studies had to include at least two interventions included in the scope of the project or form part of a network of evidence, thus permitting inclusion of placebo and adefovir.
- In terms of patient characteristics the criteria were similar to the other sets of criteria, in that only patients with compensated CHB liver disease were eligible, and transplant patients and those co-infected were ineligible.
- Only RCTs were eligible, whilst conference abstracts were excluded (unless derived from a published RCT). Although not stated in the criteria, clinical study reports held by the manufacturer were included (as evident from the flow diagram in MS appendix 8.4, page 9).
- Results from studies were only included if the HBeAg status of the patient population for a reported end-point was stated or could be inferred. It is stated that studies must report at least one of the required outcome measures at either one or three years. It is not clear why these time points were chosen (as opposed to year one or two), and no list of outcomes is specified although it is presumed that the list of outcomes in the decision problem was used.

A QUOROM flow chart is presented showing the inclusion / exclusion of studies at different stages of the review process (MS Appendix 8.4.2, page 9). The starting point is the 110 studies identified through the systematic review of entecavir for CHB (see above). (NB. The ERG queried whether this figure should be 109, and the manufacturer clarified that the figure 110 was a typographical error – see Appendix 1, A19). A further seven clinical study reports were also

added. Application of the criteria resulted in 21 RCTs being included in the MTC (NB. The ERG queried this with the manufacturer, and believe the actual figure to be 19, see section 3.1.2.1). The ERG has not independently checked to assess whether all of the RCTs appear to meet the inclusion criteria set by the manufacturer.

A breakdown of the number of studies excluded by reason is given (91 articles and 2 clinical study reports, see MS Appendix 8.4.2, page 9), but a bibliographical listing of each study together with the reason for exclusion was not included. The ERG requested such a listing but the manufacturer replied that this was not feasible within the timeframe (see Appendix 1, A6). The biggest proportion of exclusions was due to study design not being an RCT (n=42).

Inclusion criteria for systematic review of licensed therapies for chronic hepatitis B (MS Appendix 8.3)

Appendix 8.3 of the MS reports a slightly different set of inclusion / exclusion criteria for the systematic review of all licensed therapies for CHB. This was undertaken to enable the manufacturer to replicate the search strategy used by SHTAC in the previous assessment report for NICE on pegylated interferon alpha 2a and adefovir[7]. The strategy was extended to include entecavir, telbivudine and lamivudine, the purpose being to 'identify relevant reports for the purpose of further narrative review and possible meta-analysis' (MS Appendix 8.3, page 1). It should be noted that, with the exception of the studies also included in the systematic review of entecavir and in the MTC, none of the studies are reported to have been subjected to data extraction, appraisal or synthesis.

The criteria are similar to those specified for the systematic review of entecavir above. However,

- There is no specification as to whether entecavir (or any of the other drugs) may be used as single or combined agents, and no comparators are stated.
- In terms of study design it is stated that comparative studies and non-comparative studies with long term follow-up (greater than or equal to one year) were included. The systematic review of entecavir, as well as the MTC, restricted inclusion to RCTs in accordance with the decision problem and the scope.
- The criteria specify that both pegylated interferon 2a and 2b are eligible, when the latter is not currently licensed in the UK and is not included in the scope of the appraisal or the previous NICE appraisal of CHB. Of the 15 pegylated interferon alpha studies meeting the

inclusion criteria, at least nine evaluated pegylated interferon alpha 2b (MS Appendix 8.3, page 8). However, none of the 15 studies are actually analysed in the submission, except for two studies of pegylated interferon alpha 2a which were included in the MTC (see above). Therefore, inclusion of studies of this unlicensed drug does not appear to influence the results presented in the submission.

- It is also stated that pharmacokinetic and in vitro studies were ineligible, which was not stated in the inclusion criteria for the systematic review of entecavir, discussed above.

It is reported that 1009 'potentially useful reports' were screened on title and abstract (MS Appendix 8.3, page 2) which is the same number specified in the QUOROM flow diagram in the systematic review of entecavir (MS section 5.2.6). Of these a total of 18 entecavir studies were selected for further screening. (NB There is a discrepancy between the number of entecavir articles selected for further screening in MS section 5.2.6 and in Appendix 8.3. In the former the number specified is 18, whilst in the latter it is stated as 14 (see page 3). The ERG queried this with the manufacturer who reported that this is a typographical error and the correct figure is 18 – see Appendix 1, A16).

It is stated that titles and abstracts were screened by one reviewer, and these were checked by two other reviewers with differences resolved through discussion.

Application of these criteria resulted in 109 RCTs being included in the systematic review of licensed therapies for CHB (63 lamivudine; 15 pegylated interferon alpha; 19 adefovir; 10 entecavir and 2 telbivudine). The ERG has not independently checked to assess whether all of these appear to meet the inclusion criteria set by the manufacturer. As mentioned above, not all of these studies were actually analysed in the submission. A sub-set of five entecavir studies were included in the systematic review of entecavir (MS section 5.2.2), and a subset of 19 studies were included in the MTC (see above). A bibliography of the remaining studies is presented, but with no further detail on their characteristics or results (MS Appendix 8.3, pages 8 to 13).

A breakdown of the number of studies excluded by reason is given (MS Appendix 8.3, page 3), but a bibliographical listing of each study together with the reason for its exclusion was not included. The ERG requested such a listing but the manufacturer replied that this was not feasible within the timeframe (Appendix 1, page 3).

Inclusion criteria - summary

The manufacturer has presented three sets of inclusion criteria for application to the same set of search results. Although generally similar they are reported in slightly different ways and used for different purposes. The reporting is slightly confusing and would have benefited from a more unified inclusion/exclusion strategy reported in a more consistent manner. Nonetheless, the criteria appear to generally reflect the decision problem and the scope of the appraisal.

3.1.2.1 Identified studies

The clinical evidence section of the MS (section 5) begins with a table headed as a 'Complete list' of 12 entecavir studies. It should be noted that only a sub-set of five of these studies met the manufacturer's inclusion criteria for the systematic review. It is presumed the remainder are presented for completeness. This report will therefore focus on these five RCTs, all of which compared entecavir with lamviudine:

- **Study 014** (Chang *et al*, 2005;[10] CSR[11]). HBeAg positive and negative patients with recurrent viraemia on lamivudine. Dose ranging multi-national phase II trial.
- **Study 022** (Chang *et al*, 2006;[12] CSR[13]). HBeAg positive nucleoside-naïve patients. Multi-national phase III RCT.
- **Study 023** (Yao *et al*, 2007;[14] CSR). HBeAg positive and negative Chinese patients. Phase III RCT conducted in China.
- **Study 026** (Sherman *et al,* 2006;[15] CSR[16]). HBeAg positive lamivudine-refractory patients. Multi-national phase III RCT.
- **Study 027** (Lai *et al*, 2006;[17] CSR[18]). HBeAg negative nucleoside-naïve patients. Phase III RCT. Multi-national phase III RCT.

Studies 022 and 027 were very similar in design and patient characteristics, the key distinction between them being that the former restricted inclusion to patients with HBeAg positive CHB, whilst the latter included HBeAg negative patients. Both aimed to assess the non-inferiority and thence the superiority of entecavir compared to lamivudine. Duration of treatment was 52 weeks at which time "complete virological responders", defined as having undetectable HBV DNA by branched-chain (bDNA) assay and undetectable HBeAg (Study 022) or ALT <1.25 x the upper

limit of normal (ULN) at week 48 (Study 027), discontinued and were followed for 24 weeks. "Partial virologic responders", defined as having undetectable HBV DNA by bDNA assay and detectable HBeAg (Study 022) or ALT of at least 1.25 x ULN (Study 027), continued therapy up to week 96, or until complete virological response was achieved (Study 022). In both studies "non-responders", defined as having detectable HBV DNA by bDNA at week 48, discontinued treatment at week 52. Patients from studies 022 and 027 have been entered into an open-label long-term extension study (Study 901[19]) in which patients will be treated for up to five years (MS, page 41, Table 5.4). (See also section 3.1.2.3 of this report).

Study 023 was also similar in design to 022 and 027, but a key distinction was that it was conducted entirely within China with a mixed population of HBeAg positive and negative patients. In common with Studies 022 and 027, patients could progress to a second year of treatment according to their response at week 48. Those achieving a "consolidated response", defined as HBV DNA <0.7 milliequivalents per millilitre (ME q/ml) by bDNA assay and HBeAg negative for at least 24 weeks (weeks 24–48) and ALT <1.25 × ULN at week 48, stopped treatment at week 52 and were followed up for 24 weeks. Those exhibiting a partial response, defined as HBV DNA <0.7 MEq/mL by bDNA but not yet meeting criteria for consolidated response at week 48, continued treatment. Virological non-responders at week 48 (HBV DNA ≥0.7 MEq/mL by bDNA) discontinued at week 52. The CONSORT flow chart for this study states that 69 patients have entered the A1463-050 open-label extension study (MS section 5.3.3.3).

Study 026 was designed to test the superiority of switching to entecavir compared to continuing with lamivudine in HBeAg positive patients who had become refractory to lamivudine. Refractory was defined as any of the following:

- Persistently detectable HBV DNA by bDNA assay after at least 36 weeks lamivudine treatment
- Recurrence of detectable HBV DNA by bDNA assay on two determinations after achieving undetectable HBV DNA (by bDNA assay) on lamivudine
- Recurrence and persistence of HBV replication after discontinuing lamivudine provided that lamivudine had been reintroduced and maintained for ≥12 weeks prior to screening; or documented YMDD mutation and HBV viraemia on lamivudine regardless of duration of therapy.

The same protocol used in Study 022 applied in this study with regard to whether or not patients progressed to treatment in year two.

Study 014 was an earlier phase II RCT designed to test the efficacy and safety of three different doses of entecavir with the aim of selecting an optimal dose for further study in phase III clinical trials. Eligible patients were viraemia after at least 24 weeks of lamivudine therapy or had documented lamivudine resistance.

- Patients who achieved a virological response at week 24, defined as ≥1 $\log_{10}$ reduction in HBV DNA by bDNA assay from baseline, continued treatment to week 52.
- Patients with 'minimal' virological response (<1 $\log_{10}$ reduction in HBV DNA and ≥ 10 MEq/mL by bDNA assay at week 24) discontinued treatment and either started alternative HBV therapy or were enrolled into a rollover study of entecavir plus lamivudine combination therapy (Study AI463-901).
- Patients who achieved a "complete response" at week 48 (HBV DNA < lower limit of quantification (LLOQ) by bDNA assay, loss of HBeAg and normal ALT for HBeAg positive patients at baseline; HBV DNA < LLOQ by bDNA assay, maintenance of negative HBeAg and normal ALT for HBeAg negative patients at baseline) discontinued study therapy and were followed for up to 24 weeks.
- Patients who demonstrated a "partial response" at week 48 (HBV DNA < LLOQ by bDNA but positive for HBeAg or abnormal ALT) continued treatment for an additional 24 weeks (total of 76 weeks) or until they were enrolled into the open-label phase of this study.
- Patients who did not demonstrate response at week 48 (HBV DNA ≥ LLOQ by bDNA assay) discontinued treatment. These non-responders and subjects who had a relapse off treatment (HBV DNA ≥LLOQ by bDNA assay, or HBeAg positive, or ALT >1.5×ULN on two determinations at least 2 weeks apart after achieving complete response) could either enrol in Study AI463-901 (Study 901[19]) or start alternative anti-HBV therapy.

All five RCTs were published in academic journals and portable document format (PDF) versions of these were supplied by the manufacturer. The manufacturer also supplied clinical study reports (CSRs) for each trial in PDF form. These reports total over 1000 pages long in many cases and the ERG have not systematically assessed them in great detail.

Although the ERG has not checked every detail, the information presented in the MS systematic review seems to be representative of the information in the published journal articles (see

section 3.3.1). The CSRs contain additional information not present in the published trial reports. For example, they report outcomes for the cohort of patients who continued treatment into year two, as well as cumulative outcome data for all for all treated patients at the end of year two. The published trial reports, in contrast, only report outcomes at the end of one year of treatment (up to 48 weeks). Outcomes at year two are reported in the clinical evidence section of the MS (section 5.5) for four of the RCTs included in the manufacturer's systematic review, and are also included in the MTC. As these data have not been published in an academic journal they will not have been subjected to external peer review.

The five RCTs are described in further detail in MS section 5.3, with separate tables reporting:

- The methods used (e.g. the regimen and trial protocol; study phase; randomisation methods - see MS Table 5.3.1).
- The characteristics of the participants (e.g. trial inclusion/exclusion criteria; baseline characteristics - see MS Table 5.3.2), and the numbers of patients (e.g. number enrolled; number randomised; number treated; number who discontinued – see MS section 5.3.3). (In addition a CONSORT flow chart is provided for each of the five included RCTs showing the number of patients enrolled, the number randomised to study groups, and the number completing the various phases of the trials).
- Trial outcomes (e.g. primary and secondary outcome measures; and evidence to support the validity of the measures – with some unnecessary repetition throughout the table - see MS Table 5.3.4)).
- Statistical analyses and definitions of study groups (e.g. hypotheses; statistical tests used; sample sizes and power calculations; study withdrawal / intention to treat procedures).

The process undertaken by the manufacturer for the extraction of data from the included trials is not detailed in the MS (e.g. whether it was performed by one person and checked by a second).

An overview of the five included RCTs is provided in Table 5.2 (MS page 40). Their characteristics are summarised below in Table 1.

Table 1 Characteristics of the included entecavir RCTs

Reference	Methods	Participants	Outcomes
Study 014 (Chang *et al*, 2005[10]) (CSR[11])	*Design:* phase II, multicentre international double-blind, RCT *Interventions:* 1) entecavir 0.1mg qd 2) entecavir 0.5mg qd 3) entecavir 1mg qd 4) lamivudine 100mg qd *Duration:* 52 weeks (patients with virological response at week 24 continued treatment to week 52)	Aged ≥16 years with HBeAg negative or positive compensated CHB, lamivudine-refractory *Numbers:* 1) 47 2) 47 3) 42 4) 45 NB. Outcome data are only presented for groups 3 and 4 in the submission	*Primary:* • Proportion of patients with undetectable HBV DNA (by bDNA assay) at week 24. *Secondary:* • Proportion of patients with undetectable HBV DNA (by bDNA assay) at week 24. • Proportion of patients with undetectable HBV DNA (by PCR assay) at week 24 and week 48 • Mean reduction in HBV DNA • Proportion of HBeAg positive patients at baseline who lost HBeAg by week 48 • Proportion of HBeAg positive patients at baseline who seroconverted by week 48 • Proportion of patients with abnormal ALT at baseline who normalised at weeks 24 and 48.
Study 022 Chang *et al,* 2006[12]) (CSR[13])	*Design:* phase III, multicentre double-blind international, RCT *Interventions:* 1) entecavir 0.5mg qd 2) lamivudine 100mg qd *Duration:* 52 weeks (partial virologic responders continued until 96 weeks or until complete virologic response achieved)	Aged ≥16 years with HBeAg positive compensated CHB, treatment naïve *Numbers:* 1) 354 2) 355	*Primary:* • Proportion of patients with histological improvement at week 48 *Secondary (at week 48):* • Reduction in HBV DNA from baseline • Proportion of patients with undetectable HBV DNA (on PCR assay) • Decrease in Ishak fibrosis score • HBeAg loss; HBeAg seroconversion • Normalisation of ALT • Safety
Study 023 (Yao *et al*, 2007[14]) (CSR[20])	*Design:* phase III, multicentre double-blind Chinese, RCT *Interventions:* 1) entecavir 0.5mg qd 2) lamivudine 100mg qd *Duration:* 52 weeks (patients with partial response at week 48 but not a consolidated response continued to week 96)	Aged ≥16 years with HBeAg negative or positive compensated CHB, treatment naïve *Numbers:* 1) 258 2) 261	*Primary:* • Composite end-point – proportion of patients with both HBV DNA (on bDNA assay) and ALT response at week 48 *Secondary (at week 48):* • Mean reduction in HBV DNA (by PCR assay) • HBV DNA response (PCR assay) • HBeAg loss; HBeAg seroconversion • ALT normalisation

			• Safety
Study 026 (Sherman *et al,* 2006[15]) (CSR)[16]	*Design:* phase III, multicentre international double-blind, RCT *Interventions:* 1) entecavir 1mg qd 2) lamivudine 100mg qd *Duration:* 52 weeks (patients with partial response at week 48 but not a consolidated response continued to week 96)	Aged ≥16 years with HBeAg positive compensated CHB, lamivudine-refractory *Numbers:* 1) 141 2) 145	*Two co-primary end-points (at week 48):* • Histological improvement • Composite end-point – proportion of patients with both HBV DNA (on bDNA assay) and ALT response *Secondary (at week 48):* • HBV DNA response (by PCR assay) • Mean change in serum HBV DNA • Decrease in Ishak fibrosis score • HBeAg loss; HBeAg seroconversion • Normalisation of ALT • Safety analysis
Study 027 (Lai *et al*, 2006[17]) (CSR[18])	*Design:* phase III, multicentre double-blind international, RCT *Interventions:* 1) entecavir 0.5mg qd 2) lamivudine 100mg qd *Duration:* 52 weeks (patients with virologic response only continued until 96 weeks.	Aged ≥16 years with HBeAg negative compensated CHB, treatment naïve *Numbers:* 1) 325 2) 313	*Primary:* • Proportion of patients with histological improvement at week 48 *Secondary (at week 48):* • Reduction in HBV DNA from baseline • Proportion of patients with undetectable HBV DNA (on PCR) • Decrease in Ishak fibrosis score • Normalisation of ALT • Safety

Mixed treatment comparison (MTC)

Most of the detail of the characteristics of studies included in the MTC are provided in Appendix 8.4 of the MS. The manufacturer states that 24 studies were included in the network meta-analysis (MS Appendix 8.4 page 2). However:

- The ERG suspected this figure included multiple publications for the same trials, and queried this with the manufacturer who clarified that there were 24 reports describing 21 studies (see Appendix 1, page 6).
- On further inspection it appears that there are three publications describing the pivotal GLOBE trial of telbivudine compared to lamivudine (reference numbers 9, 14, and 16 in the bibliography in Appendix 8.4, p.24-25).
- The ERG therefore estimates the number of studies included in the MTC is 19.

- PDF files were for supplied for all but six of the 24 reports listed in the MTC bibliography (MS Appendix 8.4).

The MTC is divided into a number of networks, classified according to HBeAg status (positive / negative); and stratified by outcome measure and year. (NB. An MTC was not considered possible for the lamivudine-refractory patient group. A 'simple' indirect comparison was conducted – see section 3.1.5) The trials contributing data for each drug in each network are cited in MS Appendix 8.4.3, and the number of trials per drug are listed below (NB. Numbers of trials exceed 19 as some trials contribute data for more than one drug):

- Entecavir – data from six RCTs were included (of which five were included in the manufacturer's main assessment of clinical effectiveness, discussed above. These trials all compare entecavir with lamivudine, hence direct as well as indirect evidence was used), plus an additional unpublished phase III RCT comparing entecavir with adefovir in HBeAg positive nucleoside-naïve patients (BMS Trial A1463-079, unpublished).
- Lamivudine – data from a total of 16 RCTs were included (including data from the lamivudine comparator arms of the five entecavir RCTs included in the manufacturer's main assessment of clinical effectiveness).
- Telbivudine – data from three RCTs were included.
- Pegylated interferon alpha 2a – data from two RCTs were included.
- Adefovir in combination with lamivudine (in lamuvidine refractory patients) – data from three RCTs were included. (NB. As mentioned above, for this patient group a 'simple' indirect comparison was conducted).

The key characteristics of some, but not all, of the studies included in the MTC are tabulated in MS Appendix 8.4.6:

- 10 'non-entecavir' studies included in the MTC were tabulated in terms of key trial inclusion criteria, patient characteristics, outcomes, and efficacy results extracted for the MTC.
- The six entecavir studies are not tabulated. Five of these were already tabulated in greater detail in section 5.3 of the MS. It is not clear why the sixth study, BMS Trial A1463-079 which compares entecavir to adefovir, was not tabulated.
- The three remaining studies included in the MTC were not tabulated, and no explanation is given for this. However, it is presumed that the reason for their omission was because all of them were subsequently excluded from the MTC due to network redundancy (see MS Appendix 8.4.3).

No indication is given whether the methodology of the RCTs in the MTC was critically appraised. The ERG queried this with the manufacturer who clarified that no appraisal had been conducted (see Appendix 1).

The manufacturer makes no comment regarding how applicable the RCTs included in the MTC are to the scope of the appraisal and the decision problem. The trials, published between 1998 and 2007, were mostly drug company sponsored international phase II/III studies conducted in HBeAg positive patients. From examination of the table of study characteristics it appears that the trials predominantly featured Asian patients with compensated CHB, and excluded patients with co-infections and confounding medical conditions. Eligibility into the trials appears mainly to be on the basis of raised ALT and HBV DNA levels and histological evidence of necro-inflammation and fibrosis. Therefore, it can be taken that the trials included in the MTC appear generally to be applicable to the decision problem. However, the ERG has not systematically checked the study reports (where provided) in detail and it should be acknowledged that data are not reported consistently in the table, limiting the systematic assessment of applicability to the scope and decision problem.

There is also no discussion regarding how similar the trials are to each other. Given the time period over which they were conducted it would be reasonable to assume that there would be methodological differences as a consequence of technological innovations. For example, HBV DNA assays have evolved over recent years with lowering thresholds of viral response (detection). Some of the older trials use serum hybridization assays, whilst more recent trials use PCR and/or bDNA assays. In MS Appendix 8.4.3 it is stated that the outcome 'undetectable viral load', as reported by the various trials included in the MTC, corresponds to a threshold value of 300 copies/ML. However, it is unclear whether the assays used in some of the older trials are comparable with this threshold.

3.1.2.2 Details of any irrelevant studies that were included in the submission

The manufacturer presents a 'complete list' of RCTs comparing entecavir with other therapies' (MS Table 5.1) at the start of their clinical evidence section. The table provides brief details of the intervention / comparator, population, design, duration and objectives, but no results are

reported. No citation details are provided for these studies, other than the manufacturer's study reference number. It is not clear whether all of these trials have been completed and published. Of the 12 trials tabulated, only five actually met their inclusion criteria for systematic review. The remaining trials are excluded on factors such as insufficient duration (less than one year), and patient group (HIV/HBV co-infected patients). It is assumed that this table is presented to provide context around the more in-depth systematic review of entecavir which follows.

There do not appear to be any other irrelevant studies included in the submission.

3.1.2.3 Ongoing studies

MS section 5.2.5 provides details of on-going studies of entecavir from which additional evidence is anticipated within 12 months (NB. No publication dates given). Details of these studies are also reported in MS section 5.8 ('Non-RCT evidence').

- Study 901[19] is a long term observational study of open-label entecavir 1mg in nucleoside-naïve HBeAg positive and negative patients. The patients have entered the study following treatment in RCTs 022 (Chang *et al*)[12] and 027 (Lai *et al*)[17]. HBeAg positive patients from Study 022 will have been treated for five years, whilst HBeAg negative patients from Study 027 will have been treated over two to three years.
- The entecavir resistance cohort in which nucleoside-naïve and lamivudine-refractory patients will have been treated over a five year period. The cohort comprises patients from six entecavir clinical trials, and appears to be based, in part, on long-term data from study 901. A fuller description of long-term resistance monitoring is provided in section 3.3.1.6 of this report.
- An open-label extension study of Study 023 (Yao *et al*)[14] in HBeAg positive / negative Chinese patients, treated up to three years. (BMS Trial A1463-050).

3.1.2.4 Additional studies

The ERG did not identify any additional completed RCTs that are relevant for inclusion.

3.1.3 Description and critique of manufacturer's approach to validity assessment

The MS provides a formal appraisal of the validity of the included trials using the quality assessment criteria developed by NICE (MS section 5.3.6). It is not stated whether the appraisal was conducted independently by more than one person.

- How was allocation concealed?

Allocation concealment was reported in the MS (p. 63) as double blind for all five RCTs but without any explanation of how the treatment allocation was concealed in each study. The CSRs (not the MS) mention that study, investigational and BMS personnel were blinded to the treatment allocation (treatment codes were held in a password-protected database that could not be accessed by study personnel, investigators or subjects). CSRs (not the MS) for all five RCTs state that a pharmacist at Bristol-Myers Squibb who was not involved in the study design, analysis or assessments was given access to treatment codes to permit efficient drug distribution. Procedures for blinding liver histology specimens are reported in appendices to the CSRs, but these appendices were not provided by the manufacturer. The CSR for RCT 014 (not the MS) mentions that blinding of drugs was achieved by both drugs being administered as capsules which had the same appearance. CSRs for the remaining four RCTs (not the MS) mention that entecavir was administered in tablets and lamivudine was administered in capsules, with blinding achieved by giving each patient both a tablet and a capsule (one active, the other placebo).

- What randomisation technique was used?

The method of randomization was reported briefly in the MS for all five RCTs and involved standard procedures for central allocation of treatment codes in all of the RCTs. The level of detail given about the randomization procedure in the MS differed between the RCTs. Randomization was stratified by site in all the RCTs and also stratified by patients' HBeAg status in one of the RCTs. Detailed randomization codes are given in appendices to the CSRs but were not provided in the MS. The MS does not comment on whether the reported randomization procedures have any particular strengths or weaknesses.

- Was follow-up adequate?

The question of whether follow-up was adequate was not directly addressed in the manufacturer's critical appraisal of studies (MS, p. 63). To answer this question would require some comment on the clinical relevance of the study timescales. The critical appraisal in the MS merely states for the RCTs that follow-up was at least 76 weeks and up to 96 or 120 weeks in

partial virological responders. The ERG noted that the majority of efficacy data provided in the MS are for 48 weeks. Given the chronic nature of HBV infection and long-term therapeutic requirements, the MS might more usefully have focused on the year two data, given that (i) the year one data duplicate those that are readily available in the published literature, and (ii) the MS does not expand on existing interpretations of those year one data that have already been published.

- Were the individuals undertaking the outcome assessment aware of allocation?

It is stated in the MS that individuals undertaking the outcomes assessments were unaware of the treatment allocation, but the MS provides no explanation of how this was achieved (perhaps reflecting the nature of Question 4 (MS, p. 63) which seems to require only a yes/no answer. As mentioned above, information reported in the CSRs indicates that outcome assessors would not have been aware of the treatment allocation in any of the RCTs until unblinding.

- Was a justification of the sample size provided?

The MS reports that the sample sizes were justified for tests of non-inferiority in Studies 022, 023 and 027 and for tests of superiority in Studies 014, 023 and 026 with statistical power of 90%. However, the MS does not mention whether the assessments of superiority in RCTs 014 and 026 would have required tests of non-inferiority as a prerequisite and, if so, whether the reported sample sizes would have provided adequate statistical power for these.

- Was the design parallel-group or crossover?

The MS reports accurately that all five of the RCTs included in the systematic review had parallel designs.

- Was the RCT conducted in the UK?

The geographical locations of the five RCTs are adequately summarized in the MS. Two RCTs (022, 027) were multinational and included some patients from the UK. Two other multinational RCTs (014, 026) included European but not UK patients. The remaining RCT (023) was conducted exclusively in China.

- How do the included RCT participants compare with patients who are likely to receive the intervention in the UK?

The geographical composition of the RCTs is considered in the MS to be relevant to the cohort of patients likely to receive therapy for CHB in the UK. Both the HBeAg status of patients (positive or negative) and the provenance of the patients are relevant (both UK resident and immigrant patients receive CHB therapy in the UK). Most of the trials were multinational including European and Asian countries. The proportion of White patients in the trials varied from around 40% to 65%, and the proportion of Asian patients varied from 29% to 60% (One was exclusively in a Chinese population). The manufacturer's critical appraisal (MS, p. 64) does not comment on whether nucleoside-naïve and lamivudine-refractory patients would differ in their relevance to UK patient populations receiving CHB therapy. Although the patient population of Study 014 appears relevant to CHB therapy in the UK, the duration of dosing received by patients in this RCT was shorter (maximum 48 weeks) than in the other RCTs.

- Are the dosage regimens within those cited within the Summary of Product Characteristics?

The dosage regimens for both entecavir (0.5 mg/day or 1.0 mg/day) and lamivudine (100 mg/day) are correctly reported by the MS as being within those specified in the summaries of product characteristics.

- Were the study groups comparable?

The MS states that the study groups were comparable in each of the five RCTs but does not provide any further details. As only two of the RCTs provided p-values for baseline differences between the study groups, it is unclear to the ERG how the manufacturer deduced that the study groups were indeed comparable. The MS provides no comment on whether baseline characteristics differed between the RCTs. The ERG noted that prior interferon use was higher in Study 014 and 026 (40-55% of patients) than in Study 022, 023 and 027 (12-16% of patients) but the studies appear otherwise comparable in their baseline characteristics (other than the geographical differences mentioned previously).

- Were the statistical analyses used appropriate? Was an intention-to-treat (ITT) analysis undertaken?

The MS does not critically appraise the statistical analyses reported in the RCTs; it merely summarizes the key aspects of the analyses without adding further interpretation (MS, p. 65). It does not directly answer the question of whether the statistical analyses performed were

appropriate. An overall evaluation by the ERG of the statistical analyses reported in the MS is given below (section 3.1.5).

3.1.4 Description and critique of manufacturer's outcome selection

All of the outcome measures specified in the decision problem are presented in the manufacturer's assessment of clinical evidence, with the exception of time to treatment failure, survival (unless within the context of adverse events) and health related quality of life. These do not appear to have been outcome measures in any of the included clinical trials.

The primary outcome measure in Studies 022 and 027 was histological improvement, defined as improvement by at least two points in the Knodell necro-inflammatory score with no worsening in the Knodell fibrosis score at week 48, relative to baseline. In Study 023 a composite primary outcome was employed – the proportion of patients achieving an HBV DNA response (<0.7 MEq/ML) by bDNA assay and serum ALT <1.25 x ULN at week 48. Study 026 (Sherman *et al*; 2006[15]) employed two co-primary end-points, comprising histological improvement (as defined for Studies 022 and 027) and achievement of the composite end-point as in Study 023. In Study 014 the primary outcome was the proportion of patients who achieved undetectable HBV DNA (by bDNA assay) at week 24 (<0.7 MEq/ML).

Secondary outcome measures in the trials included reduction in HBV DNA levels from baseline to end-point; the proportion of patients achieving a viral load response or undetectable HBV DNA; decrease in the Ishak fibrosis score; HBeAg loss and seroconversion; normalisation of ALT, viral resistance; and adverse events.

Viral load (HBV DNA titre) was assessed using two quantitative analytical approaches. Branched-chain DNA (bDNA) assays have a threshold lower detection limit of around 0.7 mEq/mL. PCR-based assays, which have been developed more recently and are more sensitive, have a lower detection threshold of around 300-400 copies/mL. The ERG asked the manufacturer to clarify how comparable the thresholds are between the different assays. The manufacturer clarified that HBV DNA <0.7 mEq/mL is equivalent to 700,000 DNA copies/mL (See Appendix 1, page 3).

PCR-based assay results at 48 weeks were reported for all five RCTs (Table 6 in section 3.3.1.2), with results from bDNA assays also reported in two of the RCTs (see Table 7 in

section 3.3.1.2). Viral load as assessed by bDNA was a primary end-point in one RCT (014[10]) but was reported only at week 24 (Table 7).

The manufacturer did not provide any explanation as to the relative strengths and weaknesses of the two assay methods, nor how the thresholds for viral loads relate to disease state or treatment decisions. When viral load was included as a component of composite end-points (see section 3.3.1.5), the (less sensitive) estimate from bDNA assays was always used, without explanation. The ERG noted that in some of the manufacturer's clinical study reports (e.g. 023[20]) HBV DNA results by PCR assay are given both for <300 copies/mL and <400 copies/mL; however only the <300 copies/mL data are usually referred to in the manufacturer's submission.

3.1.5 Description and critique of the statistical approach used

The MS reports almost the same descriptions of the statistical methods used in the RCTs as reported in the published papers, but gives slightly more detail than the paper for Study 023. The published papers[12,17] and MS reported that for two RCTs (022, 027), a two-stage comparison of entecavir and lamivudine was carried out for the primary end-points. First, non-inferiority of entecavir compared to lamivudine was tested. If non-inferiority was demonstrated, a test of superiority of entecavir over lamivudine was then carried out. The MS (but not the published paper[14]) reports that this two-stage testing of non-inferiority and superiority was also applied in RCT 023. For the remaining RCTs (014, 026) the published papers[10,15] and MS state only that a test of superiority (entecavir over lamivudine) was carried out. Non-inferiority was inferred (Studies 022, 023, 027) if the lower limit of the two-sided 95% confidence interval for the difference in proportions of subjects achieving the specified end-point was greater than -10%. Superiority was defined for only two of the RCTs. For Study 014 the definition of superiority refers only to p-values and is unclear. For Study 026, superiority of entecavir was inferred if the 97.5% confidence interval for the estimate of the treatment differences was greater than zero. In this RCT, a Bonferroni adjustment was applied for testing superiority, but no reason is given in the paper or MS.

Overall, the statistical approaches reported in the published papers and MS relating to comparisons of entecavir against lamivudine in the RCTs appear generally appropriate. However, the statistical methods are reported superficially and have not been scrutinised in detail by the ERG. Differences in mean proportions of entecavir and lamivudine treated patients

were based on confidence intervals obtained from a normal approximation to the binomial distribution (mentioned for Studies 014, 023, 026 in the MS). Differences between means of continuous variables were tested using *t*-tests based on linear regression models that were adjusted for baseline characteristics or included baseline data as covariates (mentioned for Studies 014, 022, 023, 026 in the MS). The published papers and MS state that p-values reported in Studies 022 and 027 were not adjusted for multiple testing. Multiple testing is not mentioned for Studies 023 and 026, although in the latter RCT a Bonferroni correction was applied when assessing superiority (reason unclear; see above). The published paper for Study 014, in which three doses of entecavir and one dose of lamivudine were compared,[10] stated that the 2-sided significance level of α=0.05 was adjusted for three multiple comparisons (revised α=0.0167). The MS reports only one pairwise comparison from this RCT (one of the entecavir doses (1.0 mg/day) compared against lamivudine 100 mg/day), with no mention of multiple comparisons. The ERG assumes that α=0.05 (not 0.0167 as in the paper) would have been used for this comparison, although this is not mentioned in the MS.

According to the clinical study reports, data were analysed using two approaches. Non-completing patients were included in analyses as treatment failures (NC=F approach) and as missing data (NC=M approach). The data reported in the published papers are from the NC=F analyses. The MS does not clarify which analysis method was used; it refers sporadically to NC=F analysis for only some end-points in some RCTs (MS, p. 60, p. 81). Most of the year-one data given in the MS are the same as those reported in the published papers (i.e. based on NC=F analysis). However, data reported in the MS for the Ishak fibrosis score and HBeAg loss at week 48 in Study 026 (MS, page 79) are from the NC=M analysis. It is unclear whether this inconsistency reflects a typographic error (no explanation is given in the MS). The results obtained for these end-points in Study 026 are broadly similar for both NC=F and NC=M analysis approaches (sections 3.3.1.1 and 3.3.1.3).

P-values for baseline comparisons were given in only two of the published papers (Studies 022[12] & 027[17]) and exceeded 0.05 for all the reported variables. Published papers for the remaining trials (014, 023, 026) provided baseline variance (SD) estimates for selected variables and stated narratively that the treatment groups were well balanced at baseline for demographics and disease characteristics.[10,14,15] The baseline data reported in the MS forms a small and rather inconsistent subset of the baseline data available from the published papers. The MS does not report any of the baseline p-values given in the published papers for Studies

022 and 027. Baseline Ishak fibrosis scores are reported in the papers for Studies 022 & 027 but the MS reports these data for only Study 027. Prior interferon therapy data are reported in the published papers for Studies 014, 022, 023 and 027 but the MS reports these data only for Study 023. There are typographical errors in the MS in the reporting of viral genotype for Studies 026 and 027, but these are not relevant to the ERG assessment.

Estimates of variance (SD or SE) were not reported in the MS for any of the outcomes at the end of year one (48 weeks) that were evaluated by the ERG. An estimate of variance (SE) was given in the MS for only one of the outcomes (change from baseline in HBV DNA) in one of the RCTs (014). Confidence intervals were provided inconsistently both in the published papers and the MS for outcomes at 48 weeks. For Study 014, a confidence interval was reported in the MS only for the complete virological response, whilst for Study 023 no confidence intervals were provided for any of the outcomes. For the remaining studies (022, 026, 027), the MS provides confidence intervals for most of the outcomes.

Intent-to-treat (ITT) populations were reported inconsistently among the studies and publication types. All the RCTs mentioned an ITT population in their clinical study report, but only two (023, 026) mentioned it in their published paper.[14,15] The MS mentions ITT populations for three RCTs and defines ITT for two RCTs (Table 2). In most studies (014,[11] 022,[13] 026[16] & 027[18]) the analysis population was called 'modified ITT' (mentioned in the MS (p. 60-62) for studies 022 and 026) whilst for Study 023 it was referred to simply as 'ITT' (CSR[20] and MS, p. 61). The definition of the (modified) ITT population, where given, was all randomized patients who received ≥ 1 dose of study therapy.

Table 2 Reporting of intent-to-treat (ITT) populations in the RCTs and MS

	Study	014	022	023	026	027
Published paper	ITT mentioned	no	no	yes	yes	no
	ITT defined	no	no	no	yes	no
CSR	ITT mentioned	yes	yes	yes	yes	yes
	ITT defined	no	no	no	yes	yes
MS	ITT mentioned	no	yes (p. 60)	yes (p. 61, 65)	yes (p. 61)	no
	ITT defined	no	yes (p. 60)	no	yes (p. 61)	no

The MS presents results from the five RCTs separately, with little narrative summary and no meta-analysis undertaken of any of the five included trials for any of the outcomes to elucidate any overall effects of treatment. Aside from the inconsistencies noted above, in general the data presented in the year one data in the MS reflect the data reported in the published papers. The MS corrects some minor typographical errors which appeared in the primary publication for RCT 023 (see Table 6 and Table 12 in section 3.3.1 below).

The manufacturer does not give any reasons for not undertaking a meta-analysis, but proceeds directly to a network meta-analysis (MS section 5.5). The network meta-analysis notwithstanding, a pair-wise meta-analysis of entecavir versus lamivudine might have been a useful addition to the MS particularly since the MS does not provide much in the way of a narrative summary of the overall effect. It would also have provided information about any potential statistical heterogeneity between studies.

Mixed treatment comparison (MTC)

The manufacturer reports the methodology used to conduct a network meta-analysis (NMA – used synonymously under the heading of MTC) in section 5.5, with further detail in Appendix 8.4.

Separate networks were conducted for HBeAg negative and HBeAg positive, treatment-naïve patients, at year one and year two (year two predicted probabilities are cumulative rather than annual values). It was not considered possible to create a network for lamivudine-refractory patients (see below). The characteristics of the RCTs included in the MTC have been discussed earlier in section 3.1.2.1. The five RCTs comparing entecavir with lamivudine presented in the manufacturer's systematic review (MS section 5.2.3) are included in the MTC, hence both direct and indirect evidence is used.

The model was constructed using a Bayesian hierarchical approach using WinBUGs 1.4 software (the WinBUGs code is presented in MS Appendix 8.4.1 NB. The ERG has not examined this code). A burn-in period of 10,000 simulations was used to allow convergence, followed by 10,000 simulations for estimation. Entecavir is the baseline treatment common to all analyses, and absolute probabilities were estimated using the average rate observed across the entecavir arms at baseline. A fixed treatment effect model is used. However, no discussion or

rationale is presented for use of a fixed over a random effects model except that 'this form of analysis is discussed in more detail by a number of authors' (MS Appendix 8.4, page 2), citing journal articles on the methodology of MTC models.

The primary results are presented in terms of predicted probability that each drug attains a relevant end-point. The end-points analysed were:

- Proportion of patients with undetectable viral load below the limit of quantification (LOQ) by PCR.
- Proportion of patients achieving HBeAg seroconversion (applicable to the HBeAg positive networks only)
- Proportion of patients with histological improvement
- Proportion of patients with ALT normalisation

Log odds ratios and relative risks were also presented but only in the Appendix (MS Appendix 8.4). The results of the MTC are used in the economic model to estimate the cost-effectiveness of entecavir. (see section 4.4.1.2). A summary of the results of the MTC is reported in section 3.3.1.9 of this report.

The ERG consider the strengths of the MTC are:

- That it is supported by a reasonably sound systematic review process, in terms of the search strategy (see section 3.1.1.1), reporting of inclusion/exclusion criteria (see section 3.1.2.1) and tabulation of included evidence (see section 3.1.2.1). However, note the caveats discussed earlier in section 3.1.2.1, namely, ambiguity about the number of trials that were included; absence of any quality assessment of the trials; and inconsistent tabulation of the characteristics of included studies, limiting the assessment of the applicability of the included trials to the decision problem.
- The manufacturer has reported the outcome data extracted from the clinical trials that has been entered into the MTC, for each separate network at each year for each outcome (MS Appendix 8.4.3). This permits independent verification of the data used, although the ERG has not undertaken a systematic cross-checking with the trial publications. A visual representation of the networks and the trials populating them is provided in MS Appendix 8.4.4.

The ERG consider the weaknesses of the MTC are:

- That there are relatively few studies in some of the networks. For example, only two pegylated interferon alpha 2a RCTs are included, one in HBeAg positive and one HBeAg negative patients. Consequently the HBeAg positive and HBeAg negative networks contain only one RCT each. Furthermore, in the telbivudine HBeAg negative network only one RCT has been included. The manufacturer has used outcome data for the HBeAg negative sub-group from the GLOBE trial, a trial which had a mixed population of positive and negative patients. No discussion is given for the potential shortcomings of sub-group selection.
- There is a paucity of outcome data for year two treatment. The entecavir year two data are unpublished and will not have been subjected to the external journal peer review that the data from the other trials included in the MTC will have undergone. Pegylated interferon alpha 2a is omitted entirely from the network as no year two data were identified. Histological response to all interventions at year two was also omitted from the analysis due to lack of data.
- There is no definition of the criteria by which entecavir is judged to be 'significantly better' or 'equivalent' to other drugs.
- There is no assessment, or at the very least discussion, of heterogeneity (statistical or otherwise). The ERG asked the manufacturer to clarify whether heterogeneity had been assessed. The manufacturer clarified that there were insufficient data to allow a reliable estimate of a random effects variance to be obtained. (see Appendix 1).
- There is very little digest, discussion or reflection on the results of the MTC, and the methodology used to construct it in general.
- There is no discussion on how the results of the MTC compare to the results of the manufacturer's systematic review of entecavir (i.e. how mixed direct + indirect evidence compares with direct evidence).

Due to the issues raised above the ERG considers that results of the MTC are uncertain and should be interpreted with caution.

As mentioned earlier the MTC was only possible for nucleoside-naïve patients as it was suggested that there were insufficient data to build a network of studies in lamivudine resistant patients (see MS page 84-85). The manufacturer reports that there are relatively few clinical trials conducted in this population, and this seems a reasonable assertion. A 'simple' indirect comparison was provided for these patients on MS page 85 (table 5.6.5). Three trials, all

conducted in HBeAg positive patients, are included: Study 026 (Sherman *et al* 2006[11,15]); Perrillo *et al.* (2004)[5] and Peters *et al.* (2006)[6]. Using lamivudine as a common comparator, entecavir was compared with adefovir added to lamivudine. The studies are presented side by side in a table to permit visual examination of differences between entecavir and adefovir + lamivudine. The manufacturer asserts both that entecavir and adefovir added to lamivudine are statistically superior to lamivudine alone. Beyond this observation there is very little that can be reliably concluded about the relative efficacy of the two interventions. A pair-wise statistical indirect comparison using lamivudine as a common comparator and adjusted to take into account randomisation (along the lines of that suggested by Glenny *et al* (2005)[21]), may have been possible. However, no mention of such an approach is made.

The manufacturer also presents a 'descriptive' analysis of genotypic resistance rates for the drugs in section 5.6.6 (excluding pegylated interferon alpha 2a, which is not associated with resistance). It is acknowledged that an MTC was not possible as much of the data are from long-term observational studies. The manufacturer has therefore tabulated cumulative rates of resistance up to five years of follow-up, from a variety of sources. A caveat is provided that there are differences in populations and methodologies between these evidence sources. Caution is therefore required in the interpretation of this table.

3.2 Summary statement of manufacturer's approach

- The manufacturer has reported a systematic review of RCTs of entecavir, and a mixed treatment comparison model (MTC).
- The decision problem was similar to the scope of the appraisal, with some minor discrepancies. The decision problem does not include the use of entecavir in combination with other agents. However, it is not thought that any trials of entecavir as combination therapy have been conducted.
- The clinical effectiveness searches conducted by the manufacturer appear to be sound, although there were some limitations in how they have been reported. All of the databases recommended by NICE have been searched, plus additional databases. The search was designed to inform both the systematic review of entecavir RCTs, plus the MTC of entecavir and comparator drugs. The same set of search results were screened using criteria relevant to each. Both sets of inclusion criteria reflect the decision problem. Although the ERG has

not replicated the manufacturer's searches it appears that all relevant studies are likely to have been included.

- Five RCTs were included in the manufacturer's systematic review of entecavir. All of these appear to fully meet the manufacturer's inclusion criteria. Full data extraction (albeit with some minor typographical errors – see Appendix 1) and critical appraisal has been undertaken on all of these. Journal publications are available for all five RCTs, but only present outcome data up to 48 weeks. Outcome data up to week 96 are only available from commercial in confidence clinical study reports. The RCTs appear to be of generally good methodological quality, and are relevant to the decision problem.
- It appears that 19 studies were included in the MTC (NB. the manufacturer reported that there were 21 studies). Other than the five entecavir RCTs, these trials have not been subjected to critical appraisal, and there is limited data extraction. The ERG has not fully assessed whether these trials meet the inclusion criteria for the MTC or appraised their methodological quality. The key limitations of the MTC included lack of assessment and discussion of potential heterogeneity; no definition of statistical significance values or tests; and small number of studies / single studies in some networks. The results of the MTC are uncertain and should be interpreted with caution.
- The search strategy used to identify cost-effectiveness studies appears generally sound. Most of the databases recommended by NICE have been searched, and additional databases and websites are listed.

Quality assessment

The ERG has assessed the MS for its quality as a systematic review using the questions in CRD report 4. (Table 3).

3.3 Summary of submitted evidence

The following sub-sections summarise the results of the manufacturer's systematic review of entecavir. Each outcome measure is presented in turn, followed by a summary of results from the MTC.

Table 3 Quality assessment (CRD criteria) of the MS review of entecavir studies

CRD Quality Item; score Yes/No/Uncertain with comments	
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes – inclusion criteria presented for systematic review of entecavir; MTC model; and systematic review of licensed therapies for CHB. The inter-relationship between these three sets of inclusion criteria could have been reported in a more unified and explicit way. The criteria themselves accord with the decision problem.
2. Is there evidence of a substantial effort to search for all relevant research?	Yes – searches appear generally sound.
3. Is the validity of included studies adequately assessed?	Yes – follows suggested NICE checklist
4. Is sufficient detail of the individual studies presented?	Partially • Systematic review of entecavir RCTs – characteristics and results of all five trials reported in detail. • MTC – limited details of study characteristics provided.
5. Are the primary studies summarised appropriately?	Uncertain • Systematic review of entecavir RCTs – very little synthesis of all five RCTs as a whole. The feasibility of a pair-wise meta-analysis is not discussed. • MTC – there are some limitations in the conduct and reporting of the MTC which prompts caution in the interpretation of its results.

3.3.1 Summary of results: manufacturer's systematic review

The results of the five RCTs included in the manufacturer's systematic review are summarised in the following sub-sections. The RCTs are referred to by their clinical study report code numbers (014, 022, 023, 026, 027). The data provided by the manufacturer for the first 48 weeks of each of these RCTs have all been published.[10,12,14,15,17] Data for a second year follow-up of each RCT were also provided, but have not been published. In one RCT (027) the year-2 data provided by the manufacturer are from the entecavir Summary of Product Characteristics.[8] In the remaining RCTs the year-2 data are from unpublished clinical study reports (014,[11] 022,[13] 023,[20] 026[16]). The majority of the data from the clinical study reports are marked as commercial in confidence (as indicated below).

3.3.1.1 Histological response

Three of the RCTs reported histological improvement at 48 weeks relative to baseline, defined as an decrease in the Knodell inflammatory score ≥ 2 points without concomitant increase (>1 point) in the Knodell fibrosis score (Table 4). In these RCTs, histological improvement was the primary (022[12], 027[17]) or a co-primary end-point (026[15]). In studies 022 and 027 the criterion for non-inferiority was met with respect to this outcome. The analyses then proceeded to testing for superiority. A significantly greater proportion of entecavir-treated than lamivudine-treated patients exhibited histological improvement in all cases, with a larger improvement in patients who received the higher entecavir dose (1.0mg/day). The same RCTs also reported improvement in the Ishak fibrosis score, defined as a decrease of ≥ 1 point at week 48 relative to baseline (

Table 5). A significant difference in the proportion of patients with improved Ishak score occurred only at the higher entecavir dose (1.0 mg/day), favouring entecavir treatment over lamivudine (RCT 026). The ERG noted that the data provided in the manufacturer's submission for this RCT (which are from an analysis in which non-completers were analysed as missing data; NC=M) differ from those given in the published paper[15] (which are from an analysis in which non-completers were analysed as treatment failures; NC=F) (section 3.1.5). However, these different analytical approaches yielded broadly similar results. No data beyond 48 weeks were given for histological improvement or Ishak fibrosis scores. Aside from the discrepancy noted above by the ERG, the histological data in the manufacturer's submission agree overall with those provided in the published papers.

Table 4 Proportion (%) of patients exhibiting histological improvement by week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]	226 / 314 (72)	195 / 314 (62)	9.9 (2.6 to 17.2)	**0.009**
	027[17]	208 / 296 (70)	174 /287 (61)	9.6 (2.0 to 17.3)	**0.01**
1.0 mg/day	026[15]	68 / 124 (55)	32 / 116 (28)	27.3 (13.6 to 40.9)	**<0.0001**

Table 5 Proportion (%) of patients exhibiting improvement in the Ishak fibrosis score by week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]	121 / 314 (39)	111 / 314 (35)	3.2 (-4.4 to 10.7)	0.41
	027[17]	107 / 296 (36)	109 / 287 (38)	[redacted]	0.65
1.0 mg/day	026[15]	[redacted] 42 / 124 (34) [c]	[redacted] 19 / 116 (16) [c]	[redacted] (6.8 to 28.2) [c]	[redacted] **0.0019** [c]

[a] Not given in the MS or published paper; extracted from the CSR[18] by the ERG.
[b] As reported in the MS; data conform to the NC=M analysis approach (non-completers analysed as missing data).
[c] As reported in the published paper[15] (data extracted by the ERG); data conform to the NC=F analysis approach (non-completers analysed as treatment failures).

3.3.1.2 Viral response

PCR-based assay results at 48 weeks were reported for all five RCTs (Table 6), with results from bDNA assays also reported in two of the RCTs (Table 7). Viral load as assessed by bDNA was a primary end-point in one RCT (014[10]) but was reported only at week 24 in the first year (Table 7). The ERG noted that in some of the manufacturer's clinical study reports (e.g. 023[20]) HBV DNA results by PCR assay are given both for <300 copies/mL and <400 copies/mL; however only the <300 copies/mL data are usually referred to in the manufacturer's submission.

Table 6 Proportion (%) of patients with undetectable HBV DNA at week 48, assayed by PCR method

Entecavir dose	Study [a]		Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]		236 / 354 (67)	129 / 355 (36)	30.3 (23.3 to 37.3)	**<0.001**
	023[14]	HBeAg+	166 / 225 (74) [b]	83 / 221 (38)	-	-
		HBeAg-	31 / 33 (94)	29 / 40 (73)	-	-
		Total	197 / 258 (76)	112 / 261 (43)	-	**<0.001**

		[redacted]	[redacted]	[redacted]	[redacted]
	027[17]	293 / 325 (90)	225 / 313 (72)	18.3 (12.3 to 24.2)	**<0.001**
1.0 mg/day	014[10] [c]	11 / 42 (26) [c]	2 / 45 (4) [c]	[redacted]	**<0.01** [c,e]
	026[15]	27 / 141 (19)	2 / 145 (1)	(11.0 to 24.5)	**<0.0001**

[a] Threshold (lower limit of quantification) <300 copies/ml of HBV DNA unless stated otherwise.
[b] Incorrectly reported as 116 / 225 (74) in the published paper[14]
[c] Threshold <400 copies/ml of HBV DNA.
[d] Not reported in the MS or published paper; extracted from the CSRs[11,20] by the ERG.
[e] Reported specifically in the CSR[11] as [redacted].

In all cases where viral load was reported at week 48, the proportion of patients with an undetectable viral load assayed by PCR (<300 or <400 copies/mL) (Table 6) or by bDNA (<0.7 mEq/mL) (Table 7) was significantly higher under 0.5 mg/day and 1.0 mg/day entecavir than 1.0 mg/day lamivudine treatment.

Table 7 Proportion (%) of patients with undetectable HBV DNA at week 48 assayed by bDNA method

Entecavir dose	Study [a]	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]	322 / 354 (91)	232 / 355 (65)	25.6 (19.8 to 31.4)	**<0.001**
	027[17]	309 / 325 (95)	279 / 313 (89)	5.9 (1.8 to 10.1)	**0.005**
1.0 mg/day	014[10] [b]	33 /42 (79) [b]	6 / 45 (13) [b]	[redacted]	**<0.0001** [b]

[a] Threshold (lower limit of quantification) <0.7 mEq/ml (700,000 copies/mL) of HBV DNA.
[b] Reported for week 24 only
[c] Not reported in the MS or published paper; extracted from the CSR[11] by the ERG.

Virological response data for year two (not shown here) were reported for four of the RCTs (022[13], 023[20], 026[16], 027[8]). Data for year two are considered confidential by the manufacturer for studies 022 (p-value only), 023 and 026 (all data). The data for year two were reported for two patient cohorts but these cohorts are not clearly and consistently defined in the MS. The ERG consulted the individual clinical study reports for clarification and presumes that the year two cohorts reported in the submission are defined as follows:

- Partial virological responders / virological-only responders: patients who exhibited a virological response but (depending on the HBeAg status of patients in the study; section 3.1.2.1) did not exhibit serological or biochemical responses;
- The cumulative proportion of patients who had ever achieved a confirmed virological response through two years of treatment in two sequential measurements, or on the last on-treatment measurement.

[redacted]

3.3.1.3 HBeAg loss/seroconversion

The proportions of patients who exhibited seroconversion (appearance of HBeAg antibody and loss of HBe antigen) by 48 weeks were reported for four of the RCTs. Seroconversion occurred in similar proportions of entecavir and lamivudine treated patients, with none of the differences statistically significant (marginal statistical significance was almost reached in one RCT with lamivudine-refractory patients,[15] in which a larger proportion of patients who received 1.0 mg/day entecavir achieved seroconversion than those who received 1.0 mg/day lamivudine) (Table 8). HBeAg loss showed a similar pattern to seroconversion, with a difference between the drugs only evident in one study with lamivudine-refractory patients. In this RCT (026), the proportion of patients achieving seroconversion by 48 weeks was significantly greater with 1.0 mg/day entecavir than 1.0 mg/day lamivudine.[15] The ERG noted that the data provided in the manufacturer's submission for this RCT (which are from an analysis in which non-completers were analysed as missing data; NC=M) differ from those given in the published paper[15] (which are from an analysis in which non-completers were analysed as treatment failures; NC=F) (section 3.1.5). However, these different analytical approaches yielded similar results (Table 9).

Table 8 Proportion (%) of patients with seroconversion at 48 weeks

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value of difference
0.5 mg/day	022[12]	74 / 354 (21)	64 / 355 (18)	2.9 (-2.9 to 8.7)	0.33
	023[14]	33 / 225 (15)	39 / 221 (18)	[redacted]	Stated NS [b]
1.0	014[10]	1 / 27 (4)	2 / 32 (6)	[redacted]	Stated NS [c]

mg/day	026[15]	11 / 141 (8)	4 / 145 (3)	5.0 (-0.1 to 10.2)	0.06

NS: not statistically significant (p>0.05)
[a] Not reported in the MS or published paper; extracted from the CSRs[11,20] by the ERG.
[b] Reported specifically in the CSR[20] as [redacted].
[c] Reported specifically in the CSR[11] as [redacted].

Table 9 Proportion (%) of patients with HBeAg loss at 48 weeks

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value of difference
0.5 mg/day	022[12]	78 / 354 (22)	70 / 355 (20)	2.3 (-3.7 to 8.3)	0.45
	023[14]	41 / 225 (18)	44 / 221 (20)	[redacted]	Stated NS [e]
1.0 mg/day	014[10]	3 / 27 (11)	3 / 32 (9)	[redacted]	Stated NS [f]
	026[15]	14 / 134 (10) [a] 14 / 141 (10) [b]	5 / 135 (4*) [a] 5 / 145 (3) [b]	[redacted]	[redacted]

[a] Data in the MS conform to the NC=M analysis approach (non-completers analysed as missing data).
[b] Data in the published paper[15] (not given in the MS; extracted by the ERG) conform to the NC=F analysis approach (non-completers analysed as treatment failures).
[c] Not reported in the MS or published paper; extracted from the CSRs by the ERG.
[d] The MS reports an incorrect confidence interval and p-value (given for the NC=F analysis instead of the NC=M analysis). The correct confidence interval and p-value have been extracted from the CSR[16] by the ERG.
[e] Reported specifically in the CSR[20] as [redacted].
[f] Reported specifically in the CSR[11] as [redacted].
* Rounded percentage reported as 3 in the MS.
NS: not statistically significant (p>0.05).

HBsAg loss by 48 weeks (an indicator of disease remission and an ultimate clinical goal), was reported for two RCTs. HBsAg loss occurred in fewer than 5% of HBeAg-positive patients overall, with no significant differences between the drugs (Table 10).

Table 10 Proportion (%) of patients with HBsAg loss at 48 weeks

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value of difference
0.5 mg/day	022[12]	6 / 354 (2)	4 / 355 (1)	0.6 (-1.2 to 2.3)	0.52
	027[17]	1 / 325 (<1)	1 / 313 (<1)	[redacted]	[redacted]

[a] Not reported in the MS or published paper; extracted from the CSR[18] by the ERG.

Year two data for seroconversion and HBeAg loss (not shown here) were reported for three of the RCTs (022[13], 023[20], 026[16]), and for the two patient cohorts as defined above (3.3.1.2): (i) Partial virological responders (virologic-only responders). (ii) The cumulative proportion of patients who had ever achieved seroconversion through two years of treatment in two

sequential measurements, or on the last on-treatment measurement. For each of the end-points, statistical information (p-values) were only reported for the latter patient cohort. Note that the patient cohorts were not defined clearly in the MS; the ERG consulted clinical study reports for clarification (as in section 3.3.1.2). The year two results for seroconversion and HBeAg loss are considered confidential by the manufacturer for three of the four RCTs.

[redacted]

3.3.1.4 Biochemical response

The proportion of patients with a biochemical response, defined as alanine aminotransferase (ALT) titre at or below threshold (1.0 × upper limit of normal) at 48 weeks was reported in all five RCTs. For all of the patient groups and for both doses of entecavir, a significantly greater proportion of entecavir than lamivudine-treated patients achieved the biochemical response, with the largest difference at the higher entecavir dose (1.0 mg/day) (Table 11). These data in the manufacturer's submission are in agreement with the data presented in the published papers.

Table 11 Proportion (%) of patients with a biochemical response at week 48

Entecavir dose	Study		Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]		242 / 354 (68)	213 / 355 (60)	8.4 (1.3 to 15.4)	**0.02**
	023[14]	HBeAg+	200 / 225 (89)	172 / 221 (78)	-	-
		HBeAg-	31 / 33 (94)	31 / 40 (78)	-	-
		Total	231 / 258 (90)	203 / 261 (78)	[redacted]	**0.0003**
	027[17]		253 / 325 (78)	222 / 313 (71)	6.9 (0.2 to 13.7)	**0.045**

1.0 mg/day	014[10] [a]	19 / 28 (68)	2 / 33 (6)	[redacted]	**<0.0001**
	026[15]	86 /141 (61)	22 / 145 (15)	51.7 (35.9 to 55.8)	**<0.0001**

[a] In Study 014 the results are for < 1.25 × upper limit of normal; results at week 48 are compared to the number of patients with abnormal baseline ALT.
[b] Not reported in the MS or published paper; extracted from the CSRs[11,20] by the ERG.

The proportion of patients with a biochemical response at year two (not shown here) was reported in four of the RCTs (022[13], 023[20], 026[16], 027[8]). The data are considered confidential by the manufacturer in studies 022 (p-value only), 026 (most data) and 023 (all data).

[redacted]

3.3.1.5 Composite ('protocol-defined' or 'complete response') end-points

Composite end-points, also referred to as 'protocol defined' or 'complete response' end-points, comprised combinations of viral response, biochemical response and/or HBeAg loss. Composite end-points were used in all five RCTs to assess patients' disease status and improvement at the end of the first year and to determine their treatment course in year two. A composite end-point was specified as the primary end-point in Study 023 and as a co-primary end-point in Study 026. The viral response component of the composite end-points was always determined by bDNA assay (not PCR-based assay), with threshold HBV DNA <700,000 copies/mL (0.7 mEq). The biochemical response component was defined as ALT titre < 1.25 × the upper limit of normal. Three composite end-points were reported in the primary studies; these differed according to which of the three components (viral, biochemical, and HBeAg loss) they included (Table 12).

The proportion of patients who achieved a complete response by week 48 as indicated by the composite end-point was usually higher for entecavir-treated than lamivudine-treated patients

(most RCTs), or did not differ between the drugs (Study 022, and HBeAg-positive patients in Study 014); in no cases was lamivudine favoured. The largest differences occurred in comparisons involving patients who received the higher entecavir dose (1.0 mg/day). Where p-values were reported, the differences between drugs were statistically significant, except among the HBeAg-positive and HBeAg-negative patient sub-groups in Study 014, which had relatively small sample sizes (Table 12).

The proportions of patients who achieved a complete (composite) response in year two (not shown here) were reported for two RCTs (022[13], 026[16]) for partial virological responders (virologic-only responders). These data (both RCTs) are considered confidential by the manufacturer.

[redacted]

Table 12 Proportion (%) of patients achieving a composite end-point at week 48

Entecavir dose	Study		End-point [a]	Entecavir	Lamivudine 100mg/day	Difference (95% CI)	P-value for difference
0.5 mg/day	022[12]		1[b]	74 / 354 (21)	67 / 355 (19)	[redacted]	[redacted]
	023[14]	HBeAg+	2	199 / 225 (88) [c]	143 / 221 (65)	-	-
		HBeAg-	2	32 / 33 (97)	31 / 40 (78)	-	-
		Total	2	231 / 258 (90)	174 / 261 (67)	[redacted]	**<0.0001**
	027[17]		2	275 / 325 (85)	245 / 313 (78)	6.4 (0.3 to 12.4)	**0.04**
1.0 mg/day	014[10]	HBeAg+	3	2 / 27 (7)	2 / 32 (6)	-	Stated NS
		HBeAg-	3	10 / 15 (67)	0 / 13 (0)	-	Stated NS
		Total	3	12 / 42 (29)	2/ 45 (4)	24.1 (8.7 to 39.6)	**<0.01** [f]
	026[15]		2	77 / 141 (55)	6 / 145 (4)	50.5 (40.4 to 60.6)	**<0.0001**
			3	13 / 141 (9)	1 / 145 (<1)	8.5 (3.6 to 13.5)	**0.0008**

[a] Definition of composite end-point:
1. HBV DNA (bDNA assay) < 0.7 MEq/mL and HBeAg loss
2. HBV DNA (bDNA assay) < 0.7 MEq/mL and ALT < 1.25× upper limit of normal
3. HBV DNA (bDNA assay) < 0.7 MEq/mL and ALT < 1.25× upper limit of normal and HBeAg loss

[b] Incorrectly reported on p. 65 of the MS; the manufacturer confirmed that the end-point definition on p. 65 of the MS is a typographical error (A9 in Appendix 1).

[c] Incorrectly reported as 119 / 225 (88) in the published paper.[14]
[d] Not given in the MS or published paper, but provided by the manufacturer (from CSR[13]) in response to a query (A10 in Appendix 1).
[e] Not given in the MS or published paper; extracted from the CSR[20] by the ERG.
[f] Reported specifically as [redacted] in the CSR.[11]
NS: not statistically significant (p>0.05).

3.3.1.6 Viral resistance

The manufacturer's submission presents entecavir resistance monitoring data up to four years. These data were obtained from patients who had been initially treated with entecavir in RCT 022,[12,13] and had then entered a four-year open-label extension study of antiviral activity and safety (Study 901). Data were also obtained from the entecavir four-year resistance monitoring programme.[22] This monitoring programme included patients from RCT 022 who had continued into Study 901, together with patients from RCTs 014, 026 and 027, and an additional RCT (015), who had also continued into Study 901. The disposition of patients in terms of how many had continued from each of these RCTs into the extension Study 901 is difficult to follow. The ERG were unable to check and appraise this in detail because the manufacturer did not submit a clinical study report for Study 901 (only a poster abstract[23] was provided). The manufacturer also did not provide any of the appendices cited in the entecavir resistance monitoring programme report[22] that describe patient flow.

Strictly, patients who entered Study 901 could be considered outside the scope of the current assessment, as they were initially administered a combination of entecavir and lamivudine before returning to entecavir monotherapy (all patients received 1.0 mg/day entecavir). The combination therapy differed depending on the provenance of patients on entry into Study 901.

- Patients from RCT 022 initially received 1.0 mg/day entecavir + 100 mg/day lamivudine then proceeded to1.0 mg/day entecavir monotherapy.
- Patients from other RCTs initially received 0.5 mg/day entecavir + 100 mg/day lamivudine, changed to 1.0 mg/day entecavir + 1.0 mg/day lamivudine, then proceeded to 1.0 mg/day entecavir monotherapy.

The median duration of the combination therapy in Study 901 was reported in the MS as 13 weeks, but without any indication of the range or variance, or whether it differed among patient groups or provenance. The duration of the subsequent entecavir monotherapy in Study 901 was only reported vaguely in the manufacturer's submission as 'long term'. The ERG noted that

some of the entecavir resistance data from Study 901 included patients (from RCT 015) who had received liver transplants. These patients are outside the scope of the current appraisal, but are not separated in a conference abstract[24] and report abstract[22] that summarize the results of Study 901, and are not mentioned in the manufacturer's submission.

As the MS concerning entecavir resistance appears to be based on information outside the scope of the current appraisal, the ERG considered resistance data in RCTs 014, 022, 023, 026 and 027 that clearly are within the scope. Unfortunately these data are limited, at most, to two years. Information available from the published papers and clinical study reports is summarized below for year one and, where available, year two of these RCTs. The ERG noted that none of the data summarised below were given in the MS report. (As the year two data come from the clinical study reports these are considered confidential.)

Resistance analysis in year one (48 weeks) was reported in four studies (014,[10] 022,[12] 026,[15] 027[17]). The procedure involved PCR amplification and sequencing to identify the nucleotide sequence of the HBV reverse transcriptase domain of the HBV polymerase gene. Emergent substitutions were identified by comparison with patients' nucleotide sequence at baseline. Resistance was deduced if patients with virologic rebound (defined as a confirmed increase in HBV DNA ≥ 1 $\log_{10}$ copy/mL from the nadir value according to PCR assay during treatment) had substitutions known to confer resistance. In two trials (022,[12] 027[17]), resistance was also verified using cell culture phenotypic assays with entecavir (in which the emergent substitutions were inserted into recombinant cell culture clones). Resistance genotyping for entecavir was reported for patients with relevant pairs of baseline and 48-week data and for those who experienced virologic rebound; resistance data for lamivudine was reported, less consistently, in three of the RCTs (Table 13).

Table 13 Patient groups analysed for anti-viral drug resistance up to week 48

Study	All available patients with paired baseline & week 48 data	Patients with virologic rebound
014[10]	entecavir, lamivudine [a]	entecavir (but n=0 for 1.0mg/day dose)
022[12]	entecavir	entecavir, lamivudine
026[15]	entecavir	entecavir
027[17]	entecavir [b]	entecavir, lamivudine

[a] Number of patients not specified [b] Used a random subset (211) of the available patients

The proportion of entecavir-treated patients who experienced virologic rebound by week 48 was low (≤2%) in all cases. A larger proportion of lamivudine-treated patients experienced virologic rebound (8% & 18%; reported in two RCTs only) (Table 14). Most of the entecavir-treated patients analysed by week 48 did not have any detectable resistance-associated substitutions. The entecavir patients with resistance-associated substitutions (7/134 overall and 2/2 virological rebound patients in one RCT) were receiving the higher entecavir dose (1.0 mg/day) (Table 15). The majority of lamivudine-treated patients who experienced virological rebound and for whom data are available (two RCTs only) had detectable resistance-associated substitutions by week 48 (Table 15).

Table 14 Number (%) of patients with virologic rebound up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day
0.5 mg/day	022[12]	6 (2)	63 (18)
	027[17]	5 (2)	25 (8)
1.0 mg/day	014[10]	0 (0)	-
	026[15]	2 (1.4)	-

Table 15 Proportion of patients with antiviral-resistant substitutions by week 48

Entecavir dose	Study [a]	Entecavir			Lamivudine 100mg/day		
		0 weeks	48 weeks [b]	Virologic rebound patients	0 weeks	48 weeks [b]	Virologic rebound patients
0.5 mg/day	022[12]	-	0 / 339 (E)	0 / 6 (E) [e]	-	-	45 / 63 (L)
	027[17]	-	0 / 211 (E)	0 / 5 (E) [e]	-	-	20 / 25 (L)
1.0 mg/day	014[10]	38 / 42 (L)	0 / 42 (E) [c]	-	39 / 45 (L)	-	-
	026[15]	118 / 141 (L)	7 / 134 (E) [d]	2 / 2 (E)	124 / 145 (L)	-	-

[a] (E): entecavir-resistant substitutions; (L): lamivudine-resistant substitutions.
[b] For patients that had paired baseline and 48-week data.
[c] 2 resistant substitutions were observed in entecavir patients on other doses (0.1 & 0.5 mg/day).
[d] none of these 7 patients experienced virologic rebound.
[e] these patients retained full sensitivity to entecavir in phenotypic assays at week 48.

[redacted]

[redacted]

Data on drug resistance in year two was only given in a clinical study report for one RCT (027[18]), and only for lamivudine-treated patients who had experienced virologic rebound (no entecavir-treated patients had experienced virologic rebound in this study in year two).

[redacted] Clinical study reports for the other RCTs mention that further resistance data may be available in other unpublished reports. However, these reports were not submitted by the manufacturer and are not accessible to the ERG.

3.3.1.7 Adverse events

Adverse events up to 48 weeks were reported in all five of the RCTs included in the manufacturer's systematic review. The proportions of patients with any adverse events (Table 16), or serious adverse events (Table 17) were similar for entecavir (either dose) and lamivudine. The number of deaths during treatment was low (<1% in all cases) (Table 18). Statistical tests, which were reported only in two of the RCTs, indicated no significant differences between the drugs in the frequency or seriousness of adverse events, or the frequency of deaths (p>0.3 in all comparisons).

The proportion of patients who withdrew during the first year due to adverse events was similar for entecavir and lamivudine in three RCTs (023,[14] 027,[17] 014[10]). In the remaining RCTs (022,[12] 026[15]), more lamivudine-treated than entecavir-treated patients withdrew. The difference was statistically significant in one of these RCTs,[12] but no statistics were reported in the other (Table 19).

Table 16 Proportion (%) of patients with any adverse events up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	306 / 354 (86)	297 / 355 (84)	0.34
	023[14]	154 / 258 (60)	145 / 261 (56)	-

	027[17]	246 / 325 (76)	248 / 313 (79)	0.30
1.0 mg/day	014[10]	36 / 42 (86)	38 / 45 (84)	-
	026[15]	120 / 141 (85)	117 / 145 (81)	-

Table 17 Proportion (%) of patients with serious adverse events up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	27 / 354 (8)	30 / 355 (8)	0.78
	023[14]	9 / 258 (3)	12 / 261 (5)	-
	027[17]	21 / 325 (6)	24 / 313 (8)	0.64
1.0 mg/day	014[10]	5 / 42 (12)	3 / 45 (7)	-
	026[15]	14 / 141 (10)	11 / 145 (8)	-

Table 18 Proportion (%) of deaths up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	0 / 354 (0)	2 / 355 (<1)	0.50
	023[14]	0 / 258 (0)	0 / 261 (0)	-
	027[17]	2 / 325 (<1)	0 / 313 (0)	0.50
1.0 mg/day	014[10]	0 / 42 (0)	0 / 45 (0)	-
	026[15]	1 / 141 (<1)	2 / 145 (<1)	-

Table 19 Proportion (%) of patients discontinuing due to adverse events up to week 48

Entecavir dose	Study	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	1 / 354 (<1)	9 / 355 (3)	**0.02**
	023[14]	1 / 258 (<1)	3 / 261 (1)	-
	027[17]	6 / 325 (2)	9 / 313 (3)	0.44
1.0 mg/day	014[10]	3 / 42 (7)	4 / 45 (9)	-
	026[15]	2 / 141 (1)	10 / 145 (7)	-

In all five RCTs, more lamivudine-treated than entecavir-treated patients had experienced an alanine aminotransferase (ALT) flare by week 48. However, the differences were small in 023[14] (no statistics reported) and 027[17] (p>0.3) (Table 20). The differences were larger in the

remaining RCTs (014,[10] 022,[12] 026[15]), but statistics were only reported in one of these (022,[12]). In that trial, the difference in frequency of ALT flares between drugs was statistically significant if an ALT flare was defined as ALT titre > 2× baseline and > 5× upper limit of normal (p=0.02), but not significant if an ALT flare was defined as ALT titre > 2× baseline and > 10 × upper limit of normal (p=0.08) (Table 20).

In addition to safety data for the first year of entecavir treatment, which is from the published papers[10,12,14,15,17] (as reproduced above), the manufacturer's submission also directly reproduces the safety data given in the Summary of Product Characteristics for entecavir.[8] Some of these data represent safety monitoring up to 96 or 107 weeks. However, the ERG is unable to comment on the validity of these data or their relevance to the current assessment, as the Summary of Product Characteristics does not identify the sources of its data, it provides only a superficial summary of the studies and their patients' characteristics, and it does not clearly identify the timing of the reported observations.

Table 20 Proportion (%) of patients experiencing an ALT flare up to week 48

Entecavir dose	Study	ALT flare definition [a]	Entecavir	Lamivudine 100mg/day	P-value for difference
0.5 mg/day	022[12]	1	12 / 354 (3)	23 / 355 (6)	0.08
		2	37 / 354 (10)	59 / 355 (17)	**0.02**
	023[14]	1	11 / 258 (4)	15 / 261 (6)	-
	027[17]	1	3 / 325 (<1)	5 / 313 (2)	0.50
		2	6 / 325 (2)	10 / 313 (3)	0.32
1.0 mg/day	014[10]	3	7 / 42 (17)	15 / 45 (33)	-
	026[15]	1	1 / 141 (<1)	16 / 145 (11)	-

[a] ALT flare definitions:
1. ALT > 2× baseline and > 10× upper limit of normal
2. ALT > 2× baseline and > 5× upper limit of normal
3. ALT > 2× baseline

[redacted] The safety data reported in the manufacturer's submission up to 48 weeks and the cumulative safety data reported in the clinical study reports up to the end of each study in year two are in good agreement for the five safety end-points considered above. The

number of patients in each treatment who exhibited each of these end-points in year one (Table 16 to Table 20) differed by <5% from the total number who exhibited these end-points up to the end of dosing in year two.

3.3.1.8 Health Related Quality of life

None of the five randomized controlled trials reported health related quality of life as an outcome measure

3.3.1.9 Results of the mixed treatment comparison (MTC)

Results of the MTC in nucleoside-naïve patients are reported in section 5.6.4 of the MS. Results of the 'simple' indirect comparison in lamivudine resistant patients are reported in MS section 5.6.5. Given the extreme limitations of the latter analysis (as discussed earlier – see section 3.1.5) the results will not be presented here. Similarly, a 'descriptive comparison' of cumulative genotypic resistance rates for entecavir and comparator drugs is tabulated in MS section 5.6.6. However, results are not presented in the current report.

As mentioned in section 3.1.5, there are limitations in the conduct and reporting of the MTC and its findings should be interpreted with caution. Furthermore, due to paucity of data the predicted probability of histological response for all drugs was only estimated at year one. The probability of response on any outcome for pegylated interferon alpha 2a was also only estimated at year one.

The results of the MTC suggest that entecavir is either significantly better or equivalent to comparators, depending on the outcome measure and the time-point. It is not clear, however, on what basis either of these assertions have been defined.

In HBeAg positive, treatment-naïve patients:

- HBV DNA response - entecavir had a significantly higher predicted probability at years one and two compared to all comparators.
- HBeAg seroconversion - entecavir was reported to be equivalent to all comparators in the predicted probability at both years.

- ALT normalisation - entecavir had a significantly higher predicted probability than lamivudine (at both years) and pegylated interferon alpha 2a (year one), and was reported to be 'equivalent' to telbivudine (at both years).
- Histological improvement - entecavir had a significantly higher predicted probability of compared to lamivudine at year one, and was reported to be equivalent to telbivudine (NB. pegylated interferon alpha 2a was omitted from this analysis).

Among HBeAg negative, treatment naïve patients:

- HBV DNA response - entecavir had a significantly higher predicted probability at years one and two compared with lamivudine and pegylated interferon alpha 2a, and was reported to be equivalent to telbivudine at both years.
- ALT normalisation - entecavir had a significantly higher predicted probability than all comparators at year one, but appeared similar to comparators at year two.
- Histological improvement - entecavir had a significantly higher predicted probability compared to lamivudine at year one, and was reported to be equivalent to telbivudine (NB. Pegylated interferon alpha 2a was omitted from this analysis).

The manufacturer does not make any comparison of the results of the MTC with the results of the systematic review of entecavir RCTs. Specifically, whether the results of the mixed comparison of direct and indirect evidence for entecavir versus lamivudine accord with the direct evidence for the two drugs from pair-wise comparison in RCTs. The manufacturer's review of the RCTs, as summarised in the previous sub-sections, generally show entecavir to be statistically superior to lamivudine across outcomes. In the MTC entecavir was likewise reported to be statistically superior to lamivudine, with the exception of HBeAg seroconversion where it was classed as equivalent. The head to head RCTs reported a statistically insignificant difference between the drugs on this outcome, which cannot necessarily be interpreted as equivalence.

3.4 Summary

Overall the MS provides an unbiased estimate of treatment efficacy for entecavir based on the results of the systematic review of RCTs. All five of the included RCTs compared entecavir with lamivudine. The results show that there are statistically significant differences between the two drugs favouring entecavir on most outcomes at one year of treatment. No quantitative pair-wise

meta-analysis was undertaken of these five RCTs so there is no overall estimate of treatment effect.

In order to fully address the decision problem an MTC was conducted which provided an estimate of the treatment effect of entecavir in relation to lamivudine, telbivudine, and pegylated interferon alpha 2a in nucleoside-naïve patients (NB. An MTC was not presented for the lamivudine-refractory patient group). It cannot necessarily be concluded that the MTC provides an unbiased estimate of treatment efficacy due to shortcomings in the methodology and reporting of the model (as discussed in section 3.1.5).

The manufacturer has provided an interpretation of the evidence from the systematic review and the MTC in MS section 5.9. The key assertion is that entecavir is clinically effective in nucleoside-naïve patients, with an acceptable safety profile and low rates of resistance compared with lamivudine. Based on the published RCTs this assertion would seem founded.

The manufacturer makes a number of assertions about the comparative efficacy of entecavir with the other comparators in the decision problem, based on the MTC and from non-statistical indirect comparison of cumulative resistance rates. Namely:

- Entecavir is superior in the probability of achieving undetectable viral load, and is associated with lower genotypic resistance rates compared with telbivudine in nucleoside-naïve patients.
- Entecavir is superior to pegylated interferon alpha 2a in nucleoside-naïve patients in terms of viral suppression and ALT normalisation, and equivalent in terms of HBeAg seroconversion (HBeAg positive patients only, by definition), and has a lower rate of adverse events.

The ERG suggests that these assertions are not justified based on the results of the MTC.

The MS also notes that entecavir is a more clinically effective option compared with continuing lamivudine therapy it terms of viral suppression. This is based on head-to-head RCT evidence and the ERG considers this a reasonable interpretation of the evidence. The MS states that there is a lack of data to enable the decision problem to be answered in terms of the comparative efficacy of entecavir versus adefovir added to lamivudine in lamivudine-refractory

patients. This is a reasonable assertion and the ERG do not know of any additional evidence in this patient group that is not included in the submission.

4 ECONOMIC EVALUATION

4.1 Overview of manufacturer's economic evaluation

The manufacturer's submission to NICE includes:

(i) a review of published economic evaluations of interferon alpha, pegylated interferon alpha 2a, lamivudine, adefovir and entecavir used as the first line treatment in nucleoside naïve CHB patients. The MS also reviewed economic evaluations of adefovir and entecavir as a salvage therapy in patients who became resistant to lamivudine. The search strategy to identify published literature is reported in section 6.1.1 of the MS and appraised in section 3.1.1.1. Searches were conducted between September 5th and October 10th, 2007. Appendix 8.6 of the MS presents summaries of nine studies included in the review. The ERG identified another relevant economic evaluation of entecavir vs lamivudine with adefovir as salvage therapy in HBeAg positive patients (Veenstra *et al*, 2007[25]), which was not included in the review.

(ii) a report of an economic evaluation undertaken for the NICE STA process. Entecavir as a first line treatment is compared with lamivudine, pegylated interferon alpha 2a, and telbivudine as monotherapy treatments. The cost-effectiveness of entecavir in nucleoside treatment naïve CHB patients is estimated separately for two mutually exclusive sub-groups: HBeAg positive patients and HBeAg negative patients. The base case results of the economic analysis are presented in the MS Tables 6.11-6.12 as a set of estimates of an incremental cost per QALY gained for entecavir in comparison to lamivudine, pegylated interferon alpha 2a, and telbivudine. In addition, the cost-effectiveness of entecavir vs a combination therapy of lamivudine with adefovir is estimated in HBeAg positive patients who have developed resistance to lamivudine. In this model it is implicitly assumed that entecavir is a second line (salvage) therapy in a sub-group of lamivudine-resistant patients and is compared to the alternative combination therapy of lamivudine with adefovir.

4.2 Cost effectiveness analysis (CEA) methods

The CEA consists of two Markov state transition models for HBeAg positive patients (HBeAg positive disease model) and HBeAg negative patients (HBeAg negative disease model) that

estimate the effect of treatment with entecavir and the comparators lamivudine, pegylated interferon alpha 2a, and telbivudine. Both models have a lifetime horizon and a cycle length of one year, with the half-cycle correction applied. In addition the HBeAg positive disease model is used to estimate the cost-effectiveness of entecavir vs a combination of lamivudine with adefovir in HBeAg positive patients who have developed resistance to lamivudine. The results from the economic evaluation using the HBeAg positive disease model are presented for the base case assumptions, with two years of treatment with entecavir and the comparators, except for pegylated interferon alpha 2a which is administered for one year.

The base case analysis in the HBeAg negative disease model assumes five-year treatment duration for all the therapies but pegylated interferon alpha 2a, which is administered for one year, after which the non-responding patients are switched to lamivudine for the remaining four years.

A cost-effectiveness analysis of the lifetime treatment duration is explored in the scenario analysis using the HBeAg negative disease model.

4.2.1 Natural history

The disease progression pathway adopted for the HBeAg positive disease model includes 14 mutually exclusive health states. Patients enter the model in the “chronic HBV” health state and receive entecavir or one of the comparator treatments. In accordance with the natural history of the disease, patients then may remain in this state, achieve treatment-induced response (HBeAg seroconversion), experience treatment relapse (return to CHB) or alternatively achieve HBsAg loss where the patients are effectively cured. Patients could also develop resistance to the active treatment (a virological breakthrough) with or without a severe hepatic flare (defined as ALT>10 x upper limit of normal). Patients who do not achieve HBeAg seroconversion can also enter more progressive stages of liver disease (such as active cirrhosis and decompensated cirrhosis). A specific feature of the model is an “inactive” cirrhosis health state that only HBeAg seroconverted patients could enter. This health state is associated with a significantly lower risk of decompensation than the active cirrhosis health state. All patients are assumed to be at HCC risk except for those who had experienced HBsAg loss or who received a liver transplant.

The 14 health states featured in the HBeAg positive disease model are also present in the HBeAg negative disease model. However, in the HBeAg negative sub-group of patients, treatment outcomes are defined in terms of viral suppression (e.g. undetectable viral load below the LLOQ by PCR assay). In addition, in the HBeAg negative disease model, patients may achieve response to the initial treatment, or, following a virological breakthrough, subsequently receive and respond to salvage treatment. This is reflected in two different response states (response to the initial treatment and response to salvage therapy), resulting in the total number of 15 health states in the HBeAg negative disease model.

In both models a response (either HBeAg seroconversion or an undetectable viral load in the HBeAg negative disease model) may occur spontaneously as well as being achieved in the course of treatment. All cause mortality, in addition to the mortality risk associated with CHB, was accounted for in both models.

Table 6.3 of the MS presents transition probabilities used in the natural history model for HBeAg positive and HBeAg negative sub-groups of CHB patients. Although the MS does not elaborate on the differences in the natural disease progression between the sub-groups, it can be deduced from Table 6.3 that the baseline risk of compensated cirrhosis is assumed to be higher in the HBeAg negative sub-group. This is consistent with available clinical evidence (EASL, 2003[26]) and the assumptions used in previous modelled economic evaluations of anti-CHB treatments (Shepherd *et al*, 2006)[7].

4.2.2 Treatment effectiveness

Tables 6.4 and 6.5 of the MS present treatment effects that replace the relevant natural history transition probabilities for HBeAg positive and HBeAg negative populations respectively. The estimates of response to treatment used for the base case are taken from the network meta-analyses described in section 5.6 of the MS and in Appendix 8.4.

The estimates of risks of developing resistance to active treatment came from published clinical trials (Lai *et al*, 2005 [27], Lau *et al*, 2005[28], Marcellin *et al*, 2004[29]), open-label extensions of RCT (Lee *et al*, 2006[30], Han *et al*, 2007[31]), unpublished entecavir clinical study reports (CSR[13,18,22] and observational studies (Lok *et al*, 2003[32], Di Marco *et al*, 2004[33]).

In addition, the HBeAg positive disease model and the lamivudine-refractory model use differential transition probabilities of developing compensated cirrhosis in patients who achieve viral load suppression, although they do not achieve HBeAg seroconversion. The risk is the lowest in patients treated with entecavir and the highest (almost equal to the baseline cirrhosis risk of 4.4%) in patients treated with pegylated interferon alpha 2a. The source of clinical evidence and the method of deriving relative risks for alternative treatments are presented in sections 6.2.7-6.2.8 of the MS.

The MS stated that due to the paucity of clinical effectiveness data in HBeAg positive lamivudine–refractory patients the network meta-analysis was not conducted. The estimates of clinical effectiveness of entecavir treatment (seroconversion rates, resistance rates and risk of developing compensated cirrhosis) in this sub-group were obtained from the journal publication for Study 026 (Sherman *et al*)[15], plus unpublished entecavir clinical study reports (CSR) [16 22] and an observational study (Buti *et al*, 2007)[34]. Estimates of seroconversion rates in patients treated with a combination of lamivudine and adefovir were obtained by averaging the response rates observed in two small RCTs (Peters *et al*, 2004[6], Perillo *et al*, 2004[5]).

4.2.3 Health related quality-of-life

The MS models assume that health states corresponding to the stages of natural disease progression (CHB, HBeAg seroconversion, HBsAg loss, response, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation) determine the patients' quality of life. This is consistent with approaches used in previously published economic evaluations (Wong *et al*, 1995 [35], Veestra *et al*, 2007[25], Shepherd *et al*, 2006 [7]). Utility values were obtained from a recent study by Levy *et al* (2007)[36]. In this study standard gamble utilities were elicited using an interviewer-administered survey from populations in six countries with a total of 534 CHB-infected patients and a total of 600 uninfected respondents. The sex-age adjusted utility values elicited from 100 uninfected respondents in the UK were used in the model. Details are discussed in section 4.4.1.2 of this report.

The adverse effects of pegylated interferon alpha 2a and the associated reduction in HRQoL were reflected in a utility decrement, which applied to the CHB state for the duration of therapy. This is consistent with the assumptions used in other published economic evaluations (Veenstra *et al*, 2007 [25], Wong *et al*, 1995 [35]).

4.2.4 Resources and costs

Two types of costs are used in the models: cost of medications (an initially prescribed drug and a salvage therapy whenever applicable) and the aggregated costs of monitoring and treating patients in different health states.

- Dose data were obtained from the summaries of product characteristics [37] [38] [39] [40] [41]. Unit costs for the standard doses were obtained from the most recent version of the British National Formulary[42]. The following assumptions in estimation of drug costs were used:
    - a full compliance of patients to treatment regimens;
    - the number of physician visits and investigative tests associated with active treatment was assumed to be identical across treatment groups, therefore the associated costs were not included in the model;
    - costs associated with treatment of adverse effects were also assumed to be identical across treatment groups and excluded from the model;
- Estimates of the costs of management of patients in different health states (CHB, HBeAg seroconversion, HBsAg loss, response, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation) were taken from Shepherd *et al* (2006)[7] and adjusted to 2007 price equivalents using the Gross Domestic Product (GDP) deflator. The reason for choosing the GDP deflator over the Health Service Cost Index (HSCI) is not explained in the MS. Health state costs adopted for economic evaluation reported in Shepherd *et al* (2006)[7] were "a combination of values estimated specifically for this assessment, based on treatment protocols developed with expert advisors to the project and costed with the assistance of the finance department at Southampton University Hospitals Trust, and published cost estimates for the progressive stages of liver disease".

4.2.5 Discounting

A discount rate of 3.5% was applied to both costs and outcomes at each cycle of HBeAg positive and HBeAg negative disease models.

4.2.6 Sensitivity analyses

One-way sensitivity analyses for selected variables in the base case are reported in section 6.3.3.1 of the MS. The results of probabilistic sensitivity analysis (PSA) are reported in the MS section 6.3.3.2. The MS tables 6.16 and 6.18 present a range of estimates of the probabilities of entecavir being cost-effective under the assumptions of the various threshold values for HBeAg

positive and HBeAg negative populations respectively. The means and measures of variation of costs and outcomes in the HBeAg positive population are reported in the MS Table 6.17. The MS Figures 6.5 and 6.6 show the cost-effectiveness acceptability curves (CEACs) for entecavir vs comparators pegylated interferon alpha 2a, lamivudine and telbivudine for HBeAg positive and HBeAg negative populations respectively.

4.2.7 Model validation

Approaches to validating the model are described in the MS section 6.2.14, p.133. The principal validation of the model structure and key clinical assumptions appears to have been an opinion expressed by "expert clinical hepatologists and gastroenterologists". The mathematical logic and statistical calculations appear to have been reviewed by an independent statistician and a modeller not involved in the development or analyses (though no further detail is given on the scope of this or the clinicians' review nor the criteria used to establish the model's validity).

The approach to establishing external consistency was to compare the model inputs and results with the published evaluations reviewed in section 6.1.2 of the MS.

4.2.8 Results

Consistent with the NICE reference case, results from the base case economic model are presented as incremental cost per QALY gained. For each treatment group, drug costs for the duration of treatment (two years in the HBeAg positive model and five years in the HBeAg negative model except for pegylated interferon alpha 2a, which is administered for one year in both models) are reported separately from other healthcare costs and the total lifetime costs along with the lifetime QALY gains. The results are presented in the MS Tables 6.11-6.13 for HBeAg positive, HBeAg negative populations and the population of lamivudine-refractory patients respectively. The PSA gives 95% CIs for both costs and QALYs estimated in the HBeAg positive disease model (the MS Table 6.17). The PSA of the results of the modelled economic evaluation of entecavir in HBeAg negative population were not reported and needed to be estimated by the ERG.

Table 21, Table 22 and Table 23 below summarise the results reported in Tables 6.11-6.13 and 6.17 of the MS.

Table 21 Cost effectiveness results for entecavir as first-line antiviral therapy in HBeAg-positive patients presented in the MS

	QALYs (deterministic)	Mean QALYs (PSA)(95%CI)	Total cost (deterministic)	Total mean cost (PSA)(95%CI)	ICER* (deterministic)

Entecavir	16.84	16.96 (15.42, 18.28)	£23,095	£22,705 (£19,212, £26,906)	N/A
Lamivudine	16.61	16.75 (15.44, 17.88)	£19,784	£19,506 (£16,672, £22,834)	£14,329
Peg IFN	16.64	16.75 (15.51, 17.83)	£21,396	£21,343 (£18,929, £24,136)	£8,403
Telbivudine	16.84	16.97 (15.65, 18.15)	£22,858	£22,858 (£18,109, £25,702)	Telbivudine dominant

Peg IFN=pegylated interferon alpha 2a; PSA= probabilistic sensitivity analysis; QALY=quality-adjusted life-year; ICER=incremental cost-effectiveness ratio. N/A=not applicable
*The ICER values are calculated as follows: firstly, the incremental total cost of entecavir vs a comparator is calculated and secondly, the result is divided over the incremental benefit of entecavir vs the same comparator.

Table 22 Cost effectiveness results for entecavir as first-line antiviral therapy in HBeAg-negative patients presented in the MS

	QALYs (deterministic)	Mean QALYs (PSA)(95%CI)*	Total cost (deterministic)	Total mean cost (PSA)(95%CI)*	ICER** (deterministic)
Entecavir	14.41	14.34 (12.96, 15.68)	£38,449	£38,740 (£34,837 £43,083)	N/A
Lamivudine	13.80	13.89 (12.46 15.24)	£30,270	£30,304 (£26,343, £34,756)	£13,208
Peg IFN	13.71	13.52 (12.10, 14.92)	£33,142	£33,926 (£30,021, £38,443)	£7,511
Telbivudine	14.21	14.30 (12.91, 15.61)	£37,028	£37,034 (£33,085, £41,456)	£6,907

Peg IFN=pegylated interferon alpha 2a; PSA= probabilistic sensitivity analysis; QALY=quality-adjusted life-year; ICER=incremental cost-effectiveness ratio; N/A=not applicable
*Not reported in the MS. The ERG has obtained the estimates by running a set of PSAs for each of the comparators.
** The ICER values are calculated as follows: firstly, the incremental total cost of entecavir vs a comparator is calculated and secondly, the result is divided over the incremental benefit of entecavir vs the same comparator.

Table 23 Cost effectiveness results for entecavir as salvage therapy in HBeAg-positive patients presented in the MS

	QALYs (deterministic)	Mean QALYs (PSA)(95%CI)*	Total cost (deterministic)	Total mean cost (PSA)(95%CI)*	ICER (deterministic)
Entecavir	16.43	16.42 (15.15, 17.55)	£25,114	£25,525 (£22,730 £28,770)	N/A
Adefovir/ Lamivudine	16.36	16.40 (15.16 17.50)	£26,116	£26,233 (£23,537, £29,258)	Entecavir dominant

PSA= probabilistic sensitivity analysis; QALY=quality-adjusted life-year; ICER=incremental cost-effectiveness ratio; N/A=not applicable
*Not reported in the MS. The ERG has obtained the estimates by running a PSA.

The MS summarises the results for the base case analysis stating on p.20 that entecavir is a cost effective first-line antiviral therapy in nucleoside naïve HBeAg-positive and -negative

patients with an incremental cost per additional QALY of £14,329 and £13,208, respectively when compared to lamivudine. In the analysis versus pegylated interferon alpha 2a, entecavir demonstrated cost-effectiveness with an incremental cost per additional QALY of £8,403 and £7,511 in HBeAg positive and HBeAg negative patients respectively. The MS stated on p.20 that in HBeAg positive patients, telbivudine and entecavir have similar efficacy with small difference in costs (telbivudine showing a slightly lower cost of £187 versus entecavir over a lifetime horizon). This suggests that in the base case analysis telbivudine is a dominant treatment choice in this sub-group of patients, although the PSA demonstrates that entecavir and telbivudine are comparable in this patient population. In HBeAg negative patients, entecavir was cost effective compared with telbivudine with an incremental cost per additional QALY of £6,907.

In the population of lamivudine-refractory HBeAg positive patients, comparison of entecavir with the adefovir/lamivudine combination showed that entecavir was the dominant strategy. The MS stated on p.20 that this analysis should be treated with caution due to the paucity of data in the HBeAg positive lamivudine-refractory population. A PSA for this sub-group of CHB patients does not seem to have been conducted/presented.

4.3 Critical appraisal of the manufacturer's submitted economic evaluation

4.3.1 Critical appraisal of economic evaluation methods

The ERG have considered the methods applied in the economic evaluation in the context of the critical appraisal questions listed in Table 24 below, drawn from common checklists for economic evaluation methods (e.g. Drummond *et al*, 1997).

Table 24 Critical appraisal checklist of economic evaluation

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	On page 105 the MS states that the primary aim of this economic evaluation is to estimate the cost-effectiveness of entecavir as the first-line antiviral treatment for CHB in both HBeAg-positive and -negative patients. The entecavir dose of 0.5 mg once daily is used in these patients (p.129 of the MS). The MS states that the secondary aim is to estimate the cost-effectiveness of entecavir in patients who have failed

		prior lamivudine therapy. The entecavir dose of 1.0 mg once daily is used in these patients (p.129 of the MS).
Is there a clear description of alternatives?	Yes	The MS states (p.105) that in both HBeAg-positive and -negative patients the relevant comparators for the first-line treatment for CHB are lamivudine, telbivudine and pegylated interferon alpha 2a. The MS states that the relevant comparator in patients who have failed prior lamivudine therapy is a combination of lamivudine and adefovir.
Has the correct patient group / population of interest been clearly stated?	Yes	The population of patients is correctly identified on p.106 of the MS as adults with compensated liver disease and active CHB (i.e. evidence of viral replication and active liver inflammation). The cost-effectiveness analyses of CHB treatment alternatives are reasonably conducted with respect to the sub-groups of nucleoside naïve HBeAg-positive and -negative patients and lamivudine-refractory patients.
Is the correct comparator used?	Yes	The comparators are as specified in the decision problem outlined in section 2 of the MS. section 6.2.10.1 specifies the doses for different sub-groups of CHB patients In nucleoside naïve HBeAg-positive and -negative patients the comparators and the corresponding doses are: Telbivudine 600 mg once daily; Lamivudine 100 mg once daily; Pegylated interferon alpha 2a 180 mg injection once weekly. In patients who have failed prior lamivudine therapy the dose of salvage combination therapy of lamivudine and adefovir is lamivudine 100 mg plus adefovir 10 mg once daily
Is the study type reasonable?	Yes	Cost-utility analysis is reasonable, as the major effects of successful treatment of CHB would be expected to be a reduction in mortality due to preventing further progression of liver disease and an improved quality of life.
Is the perspective of the analysis clearly stated?	Yes?	The MS states on p.108 that “the perspective of the model is the NHS and PSS, reflecting the reference case”. Also on p.20, and p.105 the MS states that the perspective of the economic evaluation is “restricted to the UK NHS and PSS and the cost-base year is 2006”. However on p.131 of the MS states that “health state costs were inflated to their 2007 price year equivalents”. The drug costs are taken from the 2007 BNF. This indicates that the base year to which costs relate is 2007 rather than 2006.
Is the perspective employed appropriate?	Yes	The MS states in section 6.2.5 that the perspective of economic evaluation is the NHS and PSS. However, it does not seem that the PSS resources/outcomes are included. As major differences between treatment groups are expected to be related to management of progression through the stages of CHB then concentration on NHS rather than PSS is appropriate. The MS states on p.108 that this perspective “potentially undervalues the therapeutic benefits and therefore the cost-effectiveness of entecavir, as patient benefits such as the ability to continue working, increased work productivity and reduced negative psychological and social symptoms due to CHB condition are excluded”. It is reasonable to suggest that

		the alleged increase in work productivity is not captured within the NICE framework, however it is likely that to some degree the treatment effect in terms of improvement in psychological and social symptoms is reflected in different estimates of the utility weights used in the model (see Table 1, Levy *et al* 2007[36])
Is effectiveness of the intervention established?	Response to treatment – Yes?	In nucleoside naïve HBeAg-positive and -negative patients the estimates of clinical effectiveness (i.e. seroconversion and suppression of HBV DNA replication respectively) were derived from the fixed effects multiple treatment comparison described in section 5.6 of the MS and Appendix 8.4. See section 3.1.5 of this report for an appraisal of the methods used.
	Cirrhosis risk reduction- Yes?	In nucleoside naïve HBeAg-positive and lamivudine-refractory patients, estimates of the reduction of risk of cirrhosis were derived from the REVEAL-HBV prospective cohort study (Iloeje *et al*, 2006)[9] in combination with viral suppression data from the network meta-analysis and published clinical trials [12 28 31 27 15 5]. Concerns are raised about validity, reliability and appropriateness of the estimates of relative risk of cirrhosis described in section 6.2.8.2 of the MS. See section 4.4.1.2 for details.
	Resistance rates- No	Estimates of the differential risks of developing resistance to active treatment came from various sources of evidence, including RCTs, open-label extensions of RCT and observational studies. These are listed in Table 6.4 and in section 6.2.8.2 of the MS. Studies other than open-label extensions of RCTs described in section 5.8 were not assessed for methodological quality. The MS states on p.86, that a formal network meta-analysis of resistance rates was not possible because the data came from non-RCTs and the patient populations were too heterogeneous. It is therefore impossible to establish the magnitude of the differences in resistance rates between the treatment groups with statistical certainty.
	No	In lamivudine-refractory patients, estimates of clinical effectiveness were derived from the simple descriptive analysis of data reported in 3 RCTs presented in Table 5.14 of the MS which was presented as an indirect comparison. It is impossible to establish the magnitude of the differences in resistance rates between the treatment groups with statistical certainty.
Has a lifetime horizon been used for analysis?	Yes	The clinical effectiveness data were only available for the short term and a model was required to extrapolate the treatment effects to the life time horizon, as is appropriate for the chronic nature of the disease. The model includes 100 cycles (i.e. 100 years).
Are the costs and consequences consistent with the perspective employed?	Yes	The model seems to have included only NHS resource use. Cost estimates are consistent with the NHS perspective. Consequences are presented as QALYs, consistent with the model perspective
Is differential timing considered?	Yes	Costs and health benefits discounted at 3.5% per year

Is incremental analysis performed?	Yes	ICERs from deterministic analysis are presented in Tables 6.11-6.13 for the base case in nucleoside naïve HBeAg-positive, HBeAg-negative and lamivudine-refractory patients respectively.
Is sensitivity analysis undertaken and presented clearly?	Yes	All variables were subject to one-way sensitivity analysis. Results of one-way sensitivity analysis of the key variables that had the greatest impact on the variability on the incremental cost/QALY results are clearly presented in Tables 6.14 and 6.15 of the MS for HBeAg-positive and -negative patients respectively. Results of probabilistic sensitivity analysis are presented in Tables 6.16 and 6.18 of the MS report for HBeAg positive and HBeAg negative populations respectively. The PSA produced a range of estimates of the probabilities of entecavir being cost effective under the assumptions of the various threshold values and for each of the comparator treatments. Tables 6.16 and 6.18 also present estimates of the probabilities of entecavir being dominant over the comparator and visa versa. MS figures 6.5 and 6.6 show the CEACs for entecavir vs comparators pegylated interferon alpha 2a, lamivudine and telbivudine for HBeAg positive and HBeAg negative populations respectively.

NICE reference case

Table 25 NICE reference case requirements

NICE reference case requirements	Included in Submission
Decision problem: As per the scope developed by NICE	Yes
Comparator: Alternative therapies routinely used in the UK NHS	Yes[a]
Perspective on costs: NHS and PSS	Yes[b]
Perspective on outcomes: All health effects on individuals	Yes
Type of economic evaluation: Cost effectiveness analysis	Yes
Synthesis of evidence on outcomes: Based on a systematic review	Yes/No[c]
Measure of health benefits: QALYs	Yes
Description of health states for QALY calculations: Use of published utility values obtained with a standardised and validated generic instrument	Yes[d]
Method of preference elicitation for health state values: Choice based method (e.g. TTO, SG, not rating scale)	Yes[e]
Source of preference data: Representative sample of the public	Uncertain[f]
Discount rate: 3.5% pa for costs and health effects	Yes

a. The comparators are: pegylated interferon alpha 2a, lamivudine, telbivudine. Appraisal of the sequential use of antiviral drugs and combination therapy, which is mentioned in the reference case, is limited to the separate sub-group analysis of lamivudine-refractory patients and to the inclusion of a combination of adefovir with an active treatment for patients developing resistance to the initial treatment in the HBeAg positive- and HBeAg negative- disease models.
b. Costs are NHS only
c. Systematic review and the fixed effects multiple treatment comparison have produced estimates of treatment response in terms of rates of seroconversion and suppression of HBV DNA replication for HBeAg-positive and HBeAg-negative nucleoside naïve patients respectively. No systematic review and evidence synthesis undertaken to estimate seroconversion rates in lamivudine-refractory patients. A systematic review and evidence synthesis was undertaken to estimate resistance rates in nucleoside naïve patients in entecavir treatment. However no systematic review of clinical evidence was conducted in relation to the comparators.

d. EQ-5D utility values for the UK population aged 35-44 years were applied to the health states corresponding to HBeAg Seroconversion and HBsAg loss. e. Use of published utility values estimated with a HRQoL instrument specifically designed for CHB (i.e. health states correspond to natural disease progression as assumed in the model) using the standard gamble method (Levy et al, 2007[36]). f. Although the study by Levy et al (2007)[36] involves a representative sample of the population from six countries, the utility values used in the model are obtained from 100 uninfected individuals residing in the UK. It is uncertain whether the sample used to elicit utility values is representative of the UK population.

N/A=not applicable

4.4 Modelling methods

An outline critical review of modelling methods has been undertaken. The review has used the framework for good practice in modelling presented by Philips *et al* (2004)[43] as a guide, addressing issues of model structure, structural assumptions, data inputs, consistency, and assessment of uncertainty.

4.4.1 Modelling approach / Model Structure

The MS presents two Markov models for the HBeAg positive and HBeAg negative variants of the disease. The models are written in Microsoft Excel and are fully executable. Inputs changed in the *'Inputs'* worksheet produce immediate changes in the results worksheet. Use of a Markov model is appropriate for chronic disease conditions such as CHB.

The MS presents schematics for the HBeAg positive and HBeAg negative disease models in Figure 6.3 and Figure 6.4 respectively. These are reproduced in

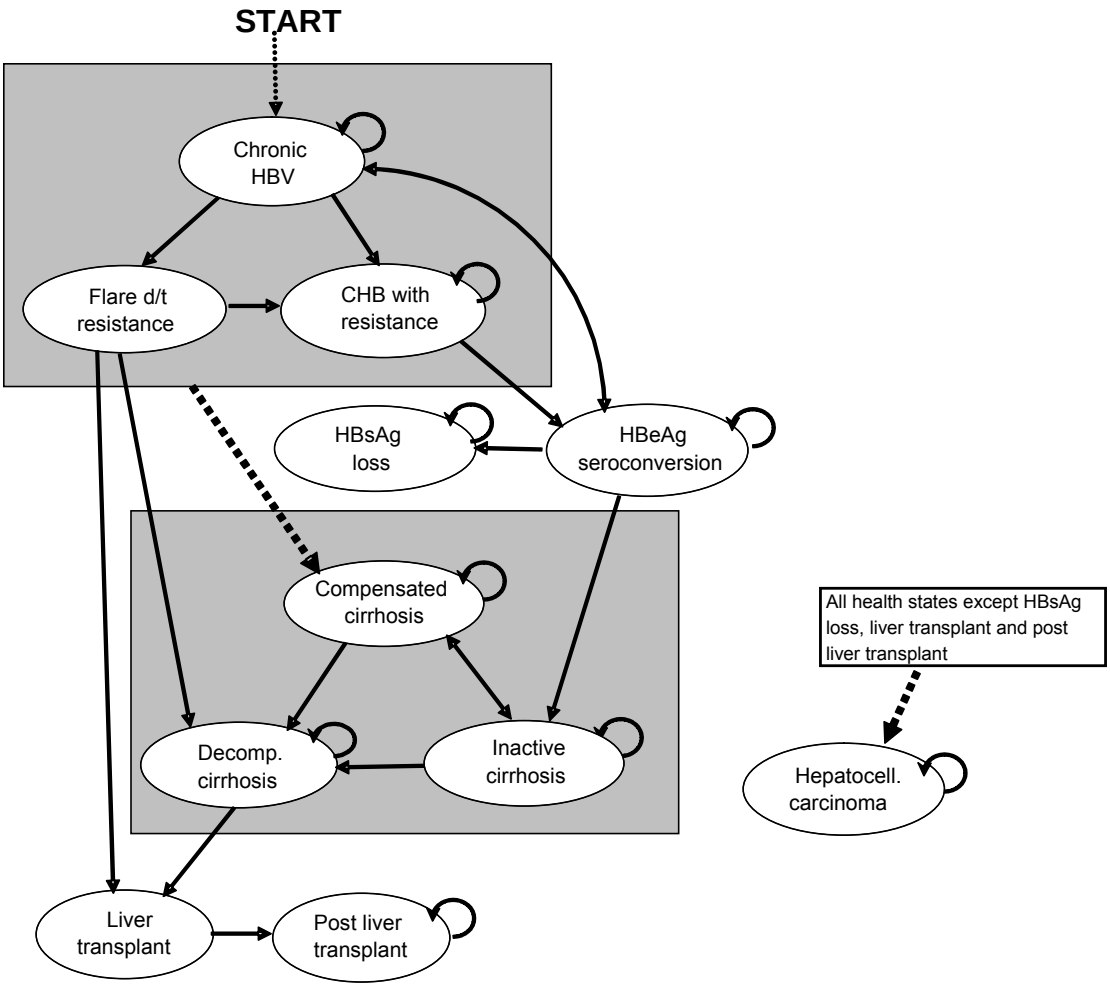
Figure 1 and

Figure 2 below. However, the schematic representations do not reflect the complexity of the models as these do not outline all the health states and all transitions. A more complete schematic of the HBeAg negative disease model only is available in the Excel spreadsheet. The inputs for the model are shown in the MS in Tables 6.3-6.5. The list of inputs is incomplete. In particular, out of six transition probabilities relating to the "Flare d/t resistance" health state (where d/t = due to), Table 6.3 shows only two, although a footnote explains how the transition probability from CHB to "Flare d/t resistance" was derived.

Figure 1 depicts the HBeAg positive disease model, which includes 14 health states although only 11 are depicted (CHB, HBeAg seroconversion, HBsAg loss, resistance, flare,

compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation).

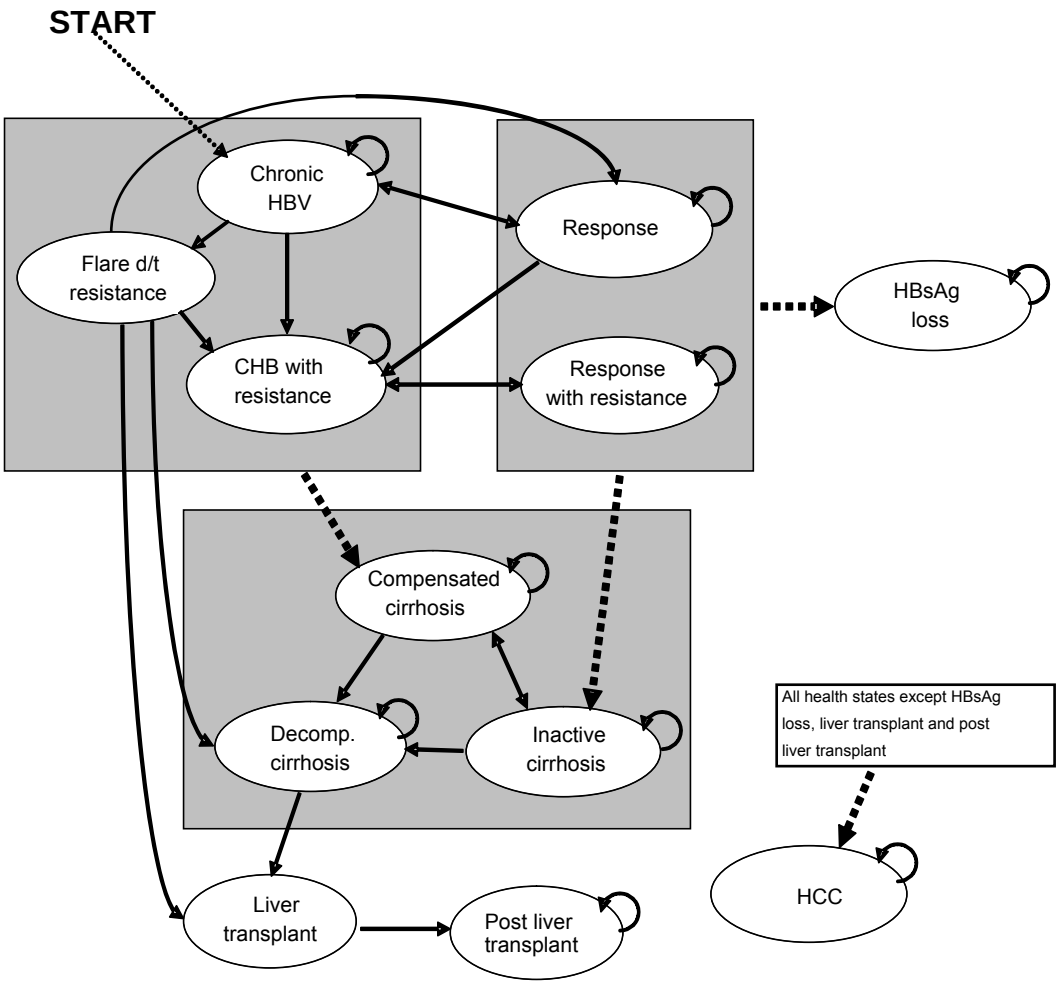
Figure 1 Schematic of the HBeAg positive disease model (reproduced from Figure 6.3 in the MS)



Both models assume complex dynamics between treatment, response and resistance to treatment. In particular, patients can achieve a response to initial treatment as well as a response to the salvage therapy prescribed to patients who subsequently develop resistance to the initial treatment. In the HBeAg negative disease model these treatment pathways are reflected in two health states representing the response to treatments (response to the initial treatment and response to the salvage therapy). Response to either the initial or the salvage

treatment may be followed by virological breakthrough resulting in the loss of response. These pathways are depicted by the arrows connecting response states with the “CHB with resistance” health state.

Figure 2 Schematic of the HBeAg negative disease model (reproduced from Figure 6.4 in the MS)



The MS does not provide a justification for the differences in the structures of the HBeAg positive and HBeAg negative disease models. In particular, the need for introducing two health states representing response in the HBeAg negative disease model (i.e. “Response” and “Response with resistance”, which is likely to be interpreted as “Response to salvage treatment”

(Figure 6.4 of the MS)) instead of a single “Response” state as in the HBeAg positive disease model was not explained.

Overall, the structure of the model is not dissimilar to those used in published economic evaluations (Shepherd *et al*, 2006[7], Veenstra *et al*, 2007 [25], Kanwal *et al*, 2005 [44]) and can be viewed as corresponding to the natural progression of the disease. However, the ERG raised a few concerns discussed below. Notwithstanding these concerns, the modelling approach and health states used in the model seem reasonable to the ERG.

4.4.1.1 Structural Assumptions

The MS indicated that a key clinical event in both models is the progression from CHB to “active” cirrhosis (this is also referred to, rather confusingly, as “compensated” cirrhosis, which can be both active and inactive.) The “inactive” cirrhosis state is occasionally referred to as a “non-replicating” state. This inconsistent labelling of the same health states has unnecessarily complicated understanding of the model. The MS provided only a partial explanation of the model schematic. In particular, the clinical rationale for including inactive in addition to compensated cirrhosis was not explained, although some clarification was provided upon request (see Appendix 1, B2-B3).

Inclusion of three different cirrhotic health states: active, inactive and decompensated, is a special feature of both models presented in the MS. The economic evaluations reviewed in section 6.1.2 of the MS conventionally include only two cirrhotic states: compensated and decompensated cirrhosis. However, a model structure, identical to the one in the MS, was recently published in a Bristol Myers Squibb funded economic evaluation of entecavir versus lamivudine with adefovir salvage in HBeAg positive patients (Veenstra *et al*, 2007[25]). The publication appeared after the manufacturer submitted that model to NICE and was not assessed in the MS.

One of the structural assumptions made in both models is that patients with response (defined either as seroconversion in the HBeAg positive disease model or viral suppression in the HBeAg negative disease model) cannot enter the state of active cirrhosis other than first entering the state of inactive cirrhosis. This assumption differs from those in previously published economic evaluations (Shepherd *et al*, 2006 [7], Veenstra *et al*, 2007[25]) where patients

with a response are assumed to have a positive, although fairly small (1%), risk of developing active/compensated cirrhosis. On the other hand, it was assumed in Kanwal *et al*, (2005)[44] (one of the cost-effectiveness studies included in the manufacturer's systematic review, see MS section 6.1) that patients with response have low rates of progression to cirrhosis (0%-0.5%) (p.W192). According to the model assumptions, inactive cirrhosis is associated with a significantly lower risk of decompensation than active cirrhosis (i.e. 0.8% vs 5%, Table 6.3 of the MS). The value of transition probability of 0.8% from inactive cirrhosis to decompensated cirrhosis was obtained from the study by Fattovich *et al* (2002)[45].

The ERG was concerned about the epidemiological data that were used to derive this probability. In response to the ERG request, clarification was received from the manufacturer stating that although the rates of decompensation were not reported separately for active and inactive cirrhotic patients in Fattovich *et al* (2002)[45], the study found that the risk of hepatic decompensation in patients with positive HBV-DNA (active cirrhosis) compared with patients with negative HBV-DNA (inactive cirrhosis) was approximately four-fold higher. This ratio was then used to convert the annualised rate of decompensation (3.1%) into the 0.8% transition probability from inactive to decompensated cirrhosis (see Appendix 1, B3). Contrary to this assertion, the ERG clinical expert felt that in patients with inactive (non-replicating) cirrhosis no further liver damage is occurring and transition from inactive cirrhosis to decompensated cirrhosis will not occur. Although the ERG has not undertaken the comprehensive validation of the underlying clinical evidence used to derive the model probability values, it is felt that the MS might have misinterpreted the results reported in Fattovich *et al* (2002)[45]. The estimate of the relative risk of decompensation in Fattovich *et al* (2002)[45] over the observation period with the median of 6.6 years seems to have been obtained while controlling for the HBV-DNA status at entry (p.2891). Some of the patients with non-replicating HBV-DNA status at baseline might still develop decompensated cirrhosis at some point during the observation period, however these patients need to become HBV-DNA-positive first (i.e. move from the inactive/non-replicating cirrhosis health state). This is consistent with the manufacturer's reply to the ERG request for clarification, which (stated that "patients with inactive disease are not likely to become cirrhotic with inflammatory response without first seroreverting or becoming HBV DNA positive" (See Appendix 1, B2). This view seems to be inconsistent with another assumption of the model which sets the value of the transition probability from inactive cirrhosis to HCC equal to the transition probability from active cirrhosis to HCC. The MS provided no clinical rationale for this assumption.

In both models patients with a response (defined either as HBeAg seroconversion in HBeAg positive patients or as an undetectable viral load in HBeAg negative patients) could enter the active/compensated cirrhosis state only via the inactive cirrhosis health state. In comparison, the previously published economic evaluations (Shepherd *et al*, 2006[7], Veenstra *et al*, 2007[25]) assumed that one percent of patients with a response can develop compensated cirrhosis. This estimate is 10 times higher than the risk of developing inactive cirrhosis in patients with a response which is estimated at 0.1% in the model. The MS indicated that this transition probability was taken from the study by Hsu *et al* (2002)[46]. In their reply to the ERG request for justification the manufacturer stated that the inactive cirrhosis state "has relatively little impact on the results of the analyses. For example, the transition probability from response/seroconversion to the inactive cirrhosis state is 0.1%; increasing this estimate by even 10-fold has little effect" (Appendix 1. B2). Although this statement is correct, the problem is not restricted to the differences in risk estimates. More important is the difference in structural assumptions, where, through the introduction of the inactive cirrhosis state, the MS model artificially slows progression of patients with response to the more advanced stages of liver disease taking an additional advantage of the differential treatment effect in the HBeAg negative model. The impact of this assumption on the results of the cost-effectiveness analysis is unclear.

The MS states on p.109 that patients could also develop antiviral drug resistance with or without a severe hepatic flare (defined as ALT>10 x upper limit of normal). No further clinical justification for introducing the "Flare due to resistance" health state was provided. In their reply to the ERG request for justification the manufacturer stated that all patients who experienced resistance should have a risk of severe flare and that the average rate of severe flare for patients with resistance across five years is approximately 2-3% per year (Lok *et al*, 2003[32]) (Appendix 1, B1(b)). Interventions without resistance (at all, or in earlier years) will not have patients moving from CHB to "Flare due to resistance" (see Appendix 1, B1(e)).
According to the model structure, patients treated for CHB can develop "Flare due to resistance" followed by transitioning to the "CHB with resistance" and receiving salvage therapy.
It remains unclear, whether:

- The direction of patient transition between the states is consistent with the course of disease. The model assumes that flares are followed by patients moving to the resistance

state, while the clarifications received from the manufacturer suggest the opposite, that patients who experienced resistance should have a risk of severe flare;
- The cycle length of one year is consistent with the average duration of flares.

In the model the annual probability of developing a severe flare (presumed to be associated with resistance) was multiplied by the probability of developing resistance to treatment. It is implicitly assumed that the treatment groups that have a reduced risk of resistance are at a lesser risk of developing “Flares due to resistance” and subsequently experiencing HCC, decompensation, and/or liver transplant. The “Flare due to resistance” health state seems to be introduced into the models to take an additional advantage of the differences in risk of developing resistance to nucleosides between the treatment groups. The effect of the modelling assumptions associated with the “Flare due to resistance” health state were tested in the ERG sensitivity analysis by assigning zero probability to the risk of experiencing “Flare due to resistance”. See section 4.4.1.5.

In the base case scenario patients are treated for two years in the HBeAg positive disease model and for five years in the HBeAg negative disease model. The duration of treatment assumed in the models is poorly justified. However, the MS also provided a scenario analysis where HBeAg negative patients receive lifetime treatment. The ERG clinical experts felt that for the majority of patients the treatment lasts longer than the two and five years assumed in the HBeAg positive and HBeAg negative disease models, respectively and that the lifetime treatment scenario for the HBeAg negative disease is the most appropriate model. The ERG explored the impact of longer treatment duration for HBeAg positive patients in scenario analysis (section 4.4.1.4)

In the MS model, only pre-cirrhotic patients receive treatment (i.e. once the patients transit to the active cirrhosis state, the treatment is terminated). However, the ERG clinical expert reviewer felt that patients who progress to the compensated cirrhosis state do not cease treatment (entecavir is not indicated for the patients with decompensated cirrhosis). Another assumption of the model is that all patients start in the CHB health state, however in practice a certain proportion of patients may first present at the stage of compensated cirrhosis. These issues are explored in the ERG sensitivity analysis (see section 4.4.1.4)

4.4.1.2 Data Inputs

Patient Groups

The cohort of HBeAg positive patients enters the Markov state transition model (HBeAg positive disease model) at 35 years of age. The patients are HBV DNA and HBeAg positive, non-cirrhotic, with elevated liver enzymes (ALT), nucleoside naïve and had received no prior CHB therapy for at least six months. The cohort of HBeAg negative patients enters the Markov state transition model (HBeAg negative disease model) at 44 years of age. The patients are HBV DNA and HBeAg-positive, non-cirrhotic, with elevated liver enzymes (ALT), nucleoside naïve and had received no prior CHB therapy for at least six months. The cohort of HBeAg positive lamivudine-resistant patients is similar to the cohort of HBeAg positive patients except that they are no longer nucleoside naïve.

The characteristics of the model populations are generally consistent with the MS decision problem, where the population is described as adults with compensated liver disease and active CHB (i.e. evidence of viral replication and active liver inflammation). However, the decision problem does not limit the CHB populations to the sub-group of non-cirrhotic patients. The assumption of the patients being non-cirrhotic at baseline does not seem to be observed in real clinical practice where a certain proportion of patients (reported to be up 10% in the entecavir RCTs systematically reviewed by the manufacturer, see MS section 5.2) present with compensated cirrhosis. In particular, HBeAg-negative patients tend to be older and have a more advanced liver disease (Lok & McMahon, 2007[47]). Therefore the populations used in the model does not completely represent those observed in practice. The model results are sensitive to the proportion of patients with compensated cirrhosis at baseline. This is explored in the ERG scenario analysis (see section 4.4.1.4 below).

Clinical Effectiveness

The MS assumes that untreated HBeAg negative patients do not achieve a spontaneous response in terms of viral load suppression, although spontaneous HBsAg loss is possible. The MS provides no clinical justification for this assumption.

The MS also assumes that 30% of HBeAg negative patients who had received antiviral treatment for five years may achieve a response (an undetectable viral load) after the treatment

termination. A small follow-up study of adefovir treated patients is quoted to support this assumption (Hadziyannis *et al*, 2006)[48]. The ERG clinical expert reviewer felt that extrapolating results of the small study of adefovir treated patients across other treatment groups creates a source of uncertainty. The ERG undertook a scenario analysis to explore the effects of different estimates of the treatment durability (see section 4.4.1.4 below).

Clinical effectiveness inputs in the model relate to the:

- HBeAg seroconversion rates in the HBeAg positive population;
- Rates of achieving an undetectable viral load as a primary clinical outcome in the HBeAg negative population, although this outcome is also included in the HBeAg positive disease model in terms of differential risks of developing compensated/active cirrhosis; and
- Risk of developing resistance to active treatment;
- HBsAg loss.

A network meta-analysis (the MTC) was undertaken to obtain the estimates of response rates in nucleoside naïve patients (HBeAg seroconversion rates in the HBeAg positive population and undetected viral load in HBeAg negative population). The response rates in the first year of treatment estimated by the MTC were used as transition probabilities in the model. The ERG considers that due to the issues raised in section 3.1.5 of this report the results of the MTC are uncertain and should be interpreted with caution. It appears, however, that the outcomes of the MTC for the first year of entecavir vs lamivudine are consistent with the results reported in the large RCTs presented in the manufacturer's systematic review of clinical effectiveness (Studies 022, 023, 027).

The MS reported the MTC estimates of clinical effectiveness results in year two (the MS Tables 5.11 and 5.13) as cumulative rather than annual values. Regardless of the methodological quality of the MTC, these results could not be used in the model. The probabilities of response in year two were derived specifically for the purposes of the Markov model. However, the method for calculating the probabilities is poorly explained in the footnote to MS Tables 6.4 and 6.5 of the MS for the HBeAg positive population and the HBeAg negative population respectively. The ERG was unable to validate the second year probabilities of response since the denominator of the formulae used for calculating response rates is the "proportion of patients who go on to year two", which was not reported in the MS (see footnotes to the MS Tables 6.4 and 6.5). It is not clear what basis for calculating the proportion of patients who

continue treatment in the second year was used (i.e. all randomised patients, treated patients, patients who completed the first year, etc.).

It appears that the average number of 82% of patients who continue treatment into the second year is used across all treatment groups in the HBeAg positive population. If this is correct, the estimated 82% of patients may be an overestimate of the proportion of patients retained in treatment after the first year (see the MS flow charts 5.3.3.2-5.3.3.4 for comparison). Also the use of an average across the groups implicitly assumes that the dropout rates across the treatment groups are independent of treatment effectiveness. This assumption does not seem to be reasonable. For example, a conservative assumption of the year two retention rates being 74% in entecavir and 59% in lamivudine (based on the Study 022 retention rate in year two calculated from the MS flow chart 5.3.3.1, page 52) would produce year two HBeAg seroconversion rates of 11.5% and 14.4% in entecavir and lamivudine groups respectively. The latter is two times higher than the clinical effectiveness rate of 7.2% reported in the MS Table 6.4.

The ERG concludes that

- methods of deriving the year two estimates of response to treatment are not clearly explained or justified;
- the estimates of response rates used in the model may bias the cost-effectiveness results in favour of entecavir.

The estimates of the risks of developing resistance to active treatment came from published clinical trials (Lai *et al*, 2005 [27], Lau *et al*, 2005[28], Marcellin *et al*, 2004[29]), open-label extensions of RCTs (Lee *et al*,2006[30], Han *et al*, 2007[31]), unpublished entecavir clinical study reports (CSR[13 18 22]) and observational studies (Lok *et al*, 2003[32], Di Marco *et al*, 2004[33]). The ERG has not undertaken a systematic cross-checking of publications used to obtain the values of transition probabilities. A systematic review of the studies reporting resistance rates associated with any of the comparator drugs does not seem to have been undertaken. The sources of clinical evidence employed to derive transition probabilities presented in section 5.6.6 of the MS do not seem to fully correspond to the sources of the clinical evidence presented in the MS Tables 6.4 and 6.5. The MS does not provide a complete assessment of the methodological quality of the clinical evidence from which these estimates of transition probabilities were extracted.

The estimates of clinical effectiveness of entecavir treatment (HBeAg seroconversion rates, resistance rates and risk of developing compensated cirrhosis) in HBeAg positive lamivudine–refractory patients were obtained from the journal publication for Study 026 (Sherman *et al* 2006)[15], plus unpublished entecavir clinical study reports (CSR[16 22]) for the entecavir treatment group. For the comparator, adefovir and lamivudine combination therapy, various published sources were employed (Perrillo *et al*. 2004[5] and Peters *et al*. 2006[6], Buti *et al*, 2007[34], Hsu *et al*, 2002[46]). As discussed in section 3.1.5 of this report, very little can be reliably concluded about the relative efficacy of the two interventions, therefore the outcomes of the cost-effectiveness analysis are uncertain.

Calculations of the estimates of the between-group difference in the risk of developing active/compensated cirrhosis in patients who did not achieve HBeAg seroconversion but nevertheless responded to treatment in terms of viral load suppression in the HBeAg positive disease model are explained in MS section 6.2.8.2. This differential effect of treatment is assumed to occur only in the first year of treatment (footnote d, Table 6.4 of the MS). This additional differential treatment effect was not discussed in the sections on clinical effectiveness in the MS. The probability estimates are based on the relationship between the viral load and the risk of cirrhosis elicited from a single prospective, population-based cohort study of untreated Taiwanese individuals with CHB (the REVEAL study)[9]. The MS does not provide a sufficient justification of the relevance of this evidence to the UK population treated for CHB. The average viral load values are extracted from various studies that were not systematically reviewed and assessed for quality (Lau *et al*, 2005[28], Han *et al*, 2007[31], Lai *et al*, 2005[27]).

Patient outcomes

The MS models assume that health states corresponding to the stages of natural disease progression (CHB, HBeAg seroconversion, HBsAg loss, response, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation) determine the patients' quality of life. This is consistent with approaches used in the previously published economic evaluations of CHB treatments (Wong *et al*, 1995[35], Veestra *et al*, 2007[25], Shepherd *et al*, 2006[7]).

Utility values were obtained from the recent study by Levy *et al* (2007)[36]. In this study standard gamble utilities were elicited using an interviewer-administered survey from populations in six

countries with a total number of 534 CHB-infected patients and a total number of 600 uninfected respondents. Utility values were obtained in relation to six CHB states: CHB, compensated cirrhosis, decompensated cirrhosis, liver transplantation, post-liver transplantation and HCC.

The age-sex adjusted utility values elicited from 100 uninfected respondents in the UK were used in the model. Although the study by Levy *et al* (2007)[36] involves a representative sample of the population from six countries, the utility values used in the model are from 100 uninfected individuals residing in the UK. It is uncertain whether the sample used to elicit utility values used in the model is representative of the UK population.

Levy *et al* (2007)[36] observed that uninfected respondents had higher mean utility values than infected respondents for most of the health states. The MS appropriately used the higher values in order to obtain the more conservative estimates of QALYs.

Utility values for HBeAg seroconversion, HBsAg loss or response states were not elicited as part of the utility study by Levy *et al*, (2007)[36]. The MS assumed these values to be no different to those of a normal individual, so the UK published tariffs on the five-dimensional European Quality of Life scale (EQ-5D) for individuals aged 35–44 years (Kind *et al*, 1999[49]) were applied to these states. The MS commented that this is consistent with utility assumptions made by Shepherd *et al* (2006)[7] for NICE TA964 (p.128 of the MS).

However, utility values in Shepherd *et al* (2006)[7] were obtained by applying the decrements, specific to each of the CHB health states to the population norms reported in Table A of Kind *et al* (1999)[49]. For example, patients in the CHB health state were assigned a decrement of 0.04 (i.e. a baseline value of 0.93 for the uninfected 31 year old individual was reduced by 0.04 to obtain the value of 0.89 which is similar to the value of 0.88 used in the model).

In the MS models the cohort of HBeAg positive patients is younger at baseline (35 years old) than the cohort of HBeAg negative patients (44 years old). There is also an age difference at baseline between the cohort of HBeAg positive patients in Shepherd *et al*, (2006)[7] (mean age 31 years) and the cohort of HBeAg negative patients (mean age 40 years). Appropriately, different baseline age-related population norms were used in these two cohorts in the model reported in Shepherd *et al*, (2006)[7]. On the contrary, age differences have not been translated in the differences in utility values used in HBeAg positive and HBeAg negative models in the

MS; the same fixed utility values were applied to each health state in the MS model regardless of the underlying age of the cohort. The approach used in Shepherd *et al* (2006)[7] seems to be more reasonable. Table 26 presents the baseline values used in the MS model and in Shepherd *et al*. (2006)[7].

Table 26 Utility values assigned to the CHB patients in different health states as reported in the MS model and in Shepherd *et al*, 2006[7]

Health state (source of the utility value estimate)	Utility values used in the MS model (Table 6.9 of the MS)	Utility values at the baseline used in the HBeAg+ve model in Shepherd *et al* (2006 p.88)	Utility values at the baseline used in the HBeAg-ve model in Shepherd *et al* (2006 p.88)
CHB (Levy *et al*, 2007)[36]	0.88	0.89	0.87
Seroconversion/Response (assumed to be equal to the population norm)	0.91	0.93	0.91
HBsAg Seroconversion (assumed to be equal to the population norm)	0.91	0.93	0.91
Flare due to resistance (assumption in the MS)	0.36	Not included in the model	Not included in the model
Resistance to treatment (assumption in the MS)	0.88	Not included in the model	Not included in the model
Active/compensated cirrhosis (Levy *et al*, 2007)[36]	0.87	0.49	0.47
Inactive cirrhosis (assumption in the MS)	0.88	Not included in the model	Not included in the model
Decompensated cirrhosis (Levy *et al*, 2007)[36]	0.36	0.39	0.37
Hepatocellular carcinoma (Levy *et al*, 2007)[36]	0.42	0.39	0.37
Liver transplant (Levy *et al*, 2007)[36]	0.69	0.38	0.36
Post-Liver transplant (Levy *et al*, 2007)[36]	0.82	0.61	0.59
Adverse events from pegIFN treatment (Veenstra *et al* 2007)[25]	0.05	Not included in the model	Not included in the model

Peg IFN =pegylated interferon alpha 2a; HBeAg+ve = HBeAg positive; HBeAg-ve = HBeAg negative;

The utility weights used in the MS models in application to the compensated cirrhosis state, liver transplant and post-liver transplant health states are markedly higher than the utility weights

used in Shepherd *et al*, (2006)[7]. The effect of these differences on the cost-effectiveness analysis of entecavir is explored in the ERG sensitivity analysis (section 4.4.1.4). The MS provides no justification for assuming the utility weight associated with the "Flare due to resistance" state as equal to the utility weight associated with decompensated cirrhosis. This may not be a reasonable assumption.

The adverse effects of pegylated interferon alpha 2a and the associated reduction in HRQoL were reflected in a utility decrement, which applied to the CHB state for the duration of therapy. This is consistent with the assumptions used in other published economic evaluations (Wong et al, 1995[35], Veestra et al, 2007[25]). Although this approach is reasonable, the reduction in utility weights does not correspond to the associated cost of treatment of adverse effects of pegylated interferon alpha 2a. In Shepherd *et al*, (2006) [7] an additional cost of physician visits and investigative tests associated with treatment of adverse events of pegylated interferon alpha 2a was included. Exclusion of these additional costs may potentially bias the cost-effectiveness estimate in favour of entecavir.

Overall the approach used in assigning utility weights to life years gained over the lifetime duration of the model seems reasonable. However, the difference between utility weights applied to the population in the compensated cirrhosis state, liver transplant and post-liver transplant health states in the MS model and the model reported in Shepherd *et al*, (2006)[7] creates a source of uncertainty. The difference in utility values between the MS models and the model in Shepherd *et al*, (2006)[7] is explained by the different methods of eliciting utilities.

Resource use

Two types of resources are used in the models: medications (initial therapy and salvage therapy whenever applicable) and the resources used in monitoring and treatment of patients in different health states. Unit costs for the standard doses of medications included in the economic evaluation were obtained from the most recent version of the British National Formulary (BNF) (issue 54, September 2007).

In nucleoside naïve HBeAg-positive and HBeAg-negative patients the initially prescribed dose of entecavir is 0.5 mg once daily. In lamivudine-refractory patients the recommended dose is 1 mg daily.

The prescribed comparator medication doses for nucleoside naïve HBeAg-positive and HBeAg-negative patients are:

- Telbivudine - 600 mg once daily;
- Lamivudine - 100 mg once daily;
- Pegylated interferon alpha 2a - 180 mg injection once weekly.

In patients who have failed prior lamivudine therapy the dose of comparator salvage therapy of lamivudine and adefovir is lamivudine 100 mg plus adefovir 10 mg once daily.

Table 27 presents the unit prices per pack and the annual costs of medication.

Table 27 Costs of the medication used in economic evaluation

Medication	Unit price per pack (£)	Annual cost in 2007 prices (£)
Entecavir 30-tablet pack 0.5 mg (1mg)	378.00	4,599*
Lamivudine 28-tablet pack 100 mg	78.09	1,018
Peg IFN 180-mg pre-filled syringe	132.06	6,339
Telbivudine 28-tablet pack 600 mg	290.33	3,785
Adefovir 30-tablet pack 10 mg	315.00	3,833

Peg IFN =pegylated interferon alpha 2a;
*the same price applies to the 30-tablet pack 1mg

Results of the calculation of the annual cost of each therapy based on the standard doses are presented in Table 6.10 of the MS and are correct.

Costs

Estimates of the costs of management of patients in different health states (CHB, HBeAg seroconversion, HBsAg loss, response, resistance, flare, compensated/active cirrhosis, inactive cirrhosis, decompensated cirrhosis, HCC, liver transplantation and post-liver transplantation) are not presented in natural units with the corresponding unit costs. The MS stated on p.129 that, where possible, health state costs were taken from the model published by Shepherd *et al*. (2006)[7] and adjusted to 2007 price equivalents using the Gross Domestic Product (GDP)

deflator. It was assumed that service provision had not changed significantly in the last two years. Costs associated with individual health states were applied for the whole duration of the model.

Health state costs adopted for economic evaluation reported in Shepherd *et al*. (2006)[7] were estimated specifically for this assessment (NICE TA964). Table 28 presents health state costs used in the MS model.

Table 28 Health state costs used in economic evaluations

Health states	Annual costs in 2007 prices (£)	Source /Assumptions
CHB	565	Shepherd *et al* (2006)
Seroconversion/Response	281	Shepherd *et al* (2006)
HBsAg Seroconversion	32	Shepherd *et al* (2006)
Flare due to resistance	9,600	Assumed to be the same as decompensated cirrhosis
Resistance to treatment	565	Assumed to be the same as CHB
Active/compensated cirrhosis	1,198	Shepherd *et al* (2006)
Inactive cirrhosis	565	Assumed to be the same as CHB
Decompensated cirrhosis	9,600	Shepherd *et al* (2006)
Hepatocellular carcinoma	8,554	Shepherd *et al* (2006)
Liver transplant	38,723	Shepherd *et al* (2006)
Post-Liver transplant	1,457	Shepherd *et al* (2006)

The MS provides no justification for assuming the costs associated with the “Flare due to resistance” state as equal to the costs associated with decompensated cirrhosis. This may not be a reasonable assumption.

4.4.1.3 Consistency

Internal consistency

Random checking has been performed for some of the key equations in the model. The ERG has not undertaken a comprehensive check of all cells in the model. The model is fully executable and inputs changed on the ‘Inputs’ worksheet produce changes in the deterministic

results (shown in the 'Results' worksheet). These can be used to replicate the results presented in the MS and the univariate sensitivity analyses for the base case model, as reported in Tables 6.11 and 6.12 in the MS. The ERG conducted sensitivity analyses to see if the results go in the right direction and at around the expected magnitude, and were satisfied that the model appeared to be consistent in this regard.

The model is generally well presented and documented and is user friendly. The model includes a worksheet that summarises the model inputs (clinical effect parameters, cost and utilities) on the 'Inputs' worksheet. The ERG view the model as a reasonable approach to modelling the cost effectiveness of entecavir, and from random checking the coding of the model appears to be accurate.

External consistency

The MS states that the external consistency of the model has been checked by consulting with clinical experts, comparing the model inputs with the previous CHB model developed by Shepherd *et al* (2006)[7] , and comparing the model results with those from previous models to check they were of a similar order. The MS claims that the results of the model are consistent with other published economic evaluations, although it does not indicate how closely the results from their model matched those of other models. Furthermore, they report that they conducted a systematic review of published economic evaluations of CHB treatment to inform assumptions within the model (see MS section 6.1 and Appendix 8.6). They mention that the model has also been reviewed by an independent statistician and modeller.

4.4.1.4 Assessment of Uncertainty

One-way sensitivity analyses

A series of one- way sensitivity analyses were carried on the base case model for all inputs in the model for the HBeAg positive and negative patients respectively. The parameters used in the one-way sensitivity analyses of entecavir versus lamivudine are shown in MS Tables 6.3, p113 and the results are shown in Table 6.14 and 6.15, p135-6 in the MS. The results shown are those parameters which have the most impact on the results. The inputs were varied around the confidence intervals for the transition probabilities, or by +/- 25% for the costs. The ranges

for treatment effectiveness varied according to the confidence interval values obtained from the MTC. However, the drug costs and the utility values were varied by only 5% and the ERG would consider varying these by more to show the uncertainty around these estimates, e.g. +/- 20%. The sensitivity analyses were presented for the entecavir versus lamivudine comparison only.

The results of the one-way sensitivity analyses versus pegylated interferon alpha 2a and telbivudine are presented in MS Appendix 8.8. The manufacturer has provided no comments on these analyses.

The models included a button 'run one way sensitivity analyses' which ran all the sensitivity analyses and ranked them in order of sensitivity of the parameters and showed these results in the 'TornadoResult' worksheet. This provided a slightly different ranking of the order of sensitivity of the parameters to that shown in Table 6.14 and 6.15.

ERG sensitivity analysis

The ERG updated the sensitivity analyses shown in the MS Table 6.14 and 6.15. The utilities and drug costs were varied by +/- 20% and this gave a slightly different ranking of the parameters from the MS as shown below in

Table 29 (HBeAg positive patients) and Table 30 (HBeAg negative patients). The model for HBeAg positive patients is most sensitive to changes in response and CHB utility rates and the transition probabilities from CHB to compensated cirrhosis and CHB to seroconversion.

The model for HBeAg negative patients is most sensitive to changes in the response rates and resistance utility, the transition probabilities between compensated cirrhosis and decompensated cirrhosis and between CHB treatment and compensated cirrhosis.

Table 29 Results of one-way sensitivity analyses for entecavir versus lamivudine as first line antiviral therapy in HBeAg positive nucleoside naive patients

		Low value		High value		
Parameters:	**Base Case**	**Value**	**ICER (£/QALY)**	**Value**	**ICER (£/QALY)**	**Range (£/QALY)**
Resistance Utility	0.88	0.70	5529	1.00	-168227	173756
CHB to CC. Baseline	0.04	0.004	48797	0.08	9541	39256
CHB Utility	0.88	0.70	-29084	1.00	7101	36185
CHB to SC, LMV, year 1	0.18	0.13	8831	0.24	28984	20152
CHB to SC, Baseline	0.09	0.06	29388	0.12	9647	19740
Discount rate, benefits	0.04	0.00	5657	0.06	24422	18765
CHB to SC, LMV, year 2	0.07	0.01	10878	0.16	23456	12578
CHB to SC, ENT, year 1	0.18	0.15	21868	0.22	9591	12276
CHB to SC, ENT, year 2	0.10	0.06	21220	0.16	9629	11591
Resist to SC, LMV, years 6+	0.09	0.06	10398	0.12	18989	8591
HBsAg- negative Utility	0.91	0.73	20047	1.00	12557	7489
Seroconversion Utility	0.91	0.73	18420	1.00	12911	5509
Discount rate, costs	0.04	0.00	12163	0.06	15123	2960
CC To DC Baseline	0.05	0.03	15956	0.07	13013	2943

CC = compensated cirrhosis; DC = decompensated cirrhosis; SC=Seroconversion (HBeAg); ENT=entecavir; LMV=lamivudine

Scenario Analysis

The MS provided additional scenario analyses to explore some the model assumptions. For the HBeAg positive model, entecavir is compared with the adefovir and lamivudine combination in a nucleoside naïve patient population and the model shows it is a dominant treatment. This was based on a non-statistical indirect comparison, and caution is therefore advised when interpreting these results

An analysis was also conducted assuming no disutility for patients receiving pegylated interferon alpha 2a treatment and the ICER increased from £8,403 to £11,899 per QALY. The MS also explored the scenario where patients received six months of consolidation therapy after HBeAg seroconversion. In this case the results were slightly less favourable than the base case but the conclusions were similar (MS Table 6.21).

Table 30 Results of one-way sensitivity analyses for entecavir versus lamivudine as first line antiviral therapy in HBeAg negative nucleoside naive patients, for lifetime treatment duration

		Low value		High value		
Parameters:	**Base Case**	**Value**	**ICER (£/QALY)**	**Value**	**ICER (£/QALY)**	**Range (£/QALY)**
Response Utility	0.91	0.73	37779	1.00	13226	24552
Discount rate, benefits	0.04	0.00	10813	0.06	23083	12270
CHB tx to CC. LMV, year 1	0.09	0.06	21504	0.12	14476	7028
Resist to CC. Active tx Baseline	0.09	0.06	20655	0.12	14808	5847
Resistance Utility	0.88	0.70	13939	1.00	19647	5708
Response to HCC	0.00	0.00	15358	0.01	21014	5656
CHBtx to CC. Entecavir	0.09	0.06	14594	0.12	20197	5603
CC Utility	0.87	0.70	14316	1.00	19417	5101
CC to DC	0.05	0.03	19750	0.07	14870	4880
Resist. Entecavir, year 4+	0.00	0.00	15349	0.01	19847	4498
CC active to HCC Baseline	0.03	0.01	19531	0.04	15232	4299
CHB to Response LMV, year 1	0.72	0.60	14900	0.82	19064	4164
Discount rate, costs	0.04	0.00	14301	0.06	17844	3543
Resist to Response salvage of lamivudine	0.60	0.49	15216	0.71	18436	3220

CC=compensated cirrhosis; DC=decompensated cirrhosis; HCC=Hepatocellular carcinoma; LMV=lamivudine; tx=treatment

For the HBeAg-negative model, lifetime treatment duration was explored in a scenario analysis as shown in Table 6.22 in the MS and in Table 31 below. In this scenario, entecavir remained cost-effective, compared with lamivudine and pegylated interferon alpha 2a, with ICERs higher than the base-case scenario of five years of treatment. Entecavir also became dominant over telbivudine.

Table 31 Cost-effectiveness results for entecavir as first-line antiviral therapy in nucleoside naïve HBeAg-negative patients (lifetime treatment duration)

	Life years	QALYs	Drug costs (£)	Healthcare costs (£)	Total costs (£)	ICER vs. entecavir (£/QALY)
Entecavir	18.34	16.42	72,923	9,351	82,274	
Lamivudine	17.63	15.58	55,574	12,586	68,160	16,850
Peg IFN	17.38	14.23	55,255	13,749	69,003	11,100
Telbivudine	17.99	16.00	81,503	11,186	92,689	Entecavir dominant

ERG scenario analysis

In the HBeAg positive model, patients with CHB were treated for two years with entecavir, lamivudine or telbivudine. The ERG's clinical advisor considered that patients would be treated for a much longer duration than two years. The ERG ran the model for longer treatment duration (Table 32). This showed that the ICER increased according to treatment duration, for example the ICER for 20 years of treatment duration was around £30,000 per QALY.

Table 32 Cost effectiveness results for entecavir versus lamivudine in HBeAg positive nucleoside naïve patients for different treatment durations

Treatment duration	Incremental QALYs	Incremental Costs	ICER (£)
2 years (Base case)	0.23	3261	14,329
5 years	0.24	5307	22,107
10 years	0.23	6170	27,120
20 years	0.22	6603	30,334

In the manufacturer's model, only pre-cirrhotic patients receive treatment (i.e. once the patients transit to the active cirrhosis state, the treatment is terminated). However, the ERG clinical expert reviewer felt that patients who progress to the compensated cirrhosis state do not cease treatment. The ERG ran the HBeAg negative model with patients with compensated cirrhosis receiving treatment for a lifetime duration, comparing entecavir with lamivudine. It was assumed that those with compensated cirrhosis receiving treatment would have a similar progression to decompensated cirrhosis, and that this transition probability would be 1.8% as used in Shepherd *et al* 2006[7] for lamivudine. In this scenario the ICER increased to £27,124 per QALY.

The MS model assumed that a certain proportion of patients receiving CHB treatment would develop flares followed by resistance to treatment. The ERG clinical expert advisor felt that this is a simplification of the actual progression of disease. The ERG also raised concerns about the uncertain direction of patients moving between flares and resistance (i.e. which comes first) and the cycle length of one year. The ERG ran the HBeAg negative model with the transition probability from CHB to "flares due to resistance" set to zero. The ICER of entecavir versus lamivudine increased slightly to £13,359 per QALY.

The MS assumed that all patients started in the CHB health state, however in practice a certain proportion of patients may first present at the stage of compensated cirrhosis. The ERG ran the HBeAg negative model with 90% of patients starting with CHB and 10% patients starting treatment with compensated cirrhosis. The ICER for entecavir vs lamivudine increased to £34,006 per QALY. When the proportion was further increased with 20% of patients starting treatment at the stage compensated cirrhosis (and 80% of patients starting with CHB) the ICER increased further to £42,608 per QALY. Treatment of patients who first present at the stage of compensated cirrhosis appears to be much less cost effective than treating patients who first present at the pre-cirrhosis state.

The ERG explored the assumptions of treatment durability in the HBeAg negative model. The MS assumed that after stopping treatment, 70% of individuals had a relapse from response to CHB. The ERG varied this between 50% and 90% for entecavir and lamivudine after treatment for five years and the ICER varied between £9,944 and £18,335 respectively.

As mentioned earlier in section 4.4.1.2, the ERG questioned the use of 7.2% for the treatment response rate in the second year with lamivudine in the HBeAg positive model, and suggests the value should be 14.4%. Using this value increased the ICER from £14,329 to £21,167 per QALY.

The manufacturer's models were run using the utility values suggested by Shepherd *et al*[7] (Table 4.6). In this case the ICER reduced from £14,329 to £10,386 and £16,850 to £11,781 in the HBeAg positive and negative models respectively. Most of the differences between the results were due to changes in the values for compensated cirrhosis.

Probabilistic Sensitivity Analysis

The MS presents a probabilistic sensitivity analysis (PSA) for the HBeAg positive and negative patients respectively (MS section 6.3.3.2). Results of the PSA for the HBeAg positive lamivudine-refractory patient population are presented in the Appendix 8.8 of the MS.

The PSA can be run from the 'Prob Outputs' worksheet by clicking on the 'Run PSA' button. It runs 10,000 iterations which takes about 20 minutes to run for the HBeAg positive model. The MS contains a scatterplot for entecavir vs telbivudine for the HBeAg positive model (Figure 6.4, p137 in MS), and cost effectiveness acceptability curves (Figures 6.5 and 6.6 in MS, p138,139) for each of the drugs for both disease models.

The parameter estimates used for the PSA were consistent with those used for the deterministic analysis. With the exception of results derived from the MTC, beta distributions are assigned to all transition probabilities and log-normal distributions to all relative risks. For results derived from the MTC, normal distributions are used to sample values for both log-odds and log-odds ratios, and these values are then used to generate the relevant transition probabilities. Drug costs are assumed to be known with certainty and thus have no associated distributions. Uncertainties surrounding health state costs are represented using log-normal distributions, with a range of +/-25% of the central estimate being used to generate 95% CIs. Uncertainties around the utility estimates are represented using beta distributions, with a range of +/-5% being used to generate 95% CIs. The distributions chosen appeared reasonable. The ERG considers that the range for utilities should be wider than 5%.

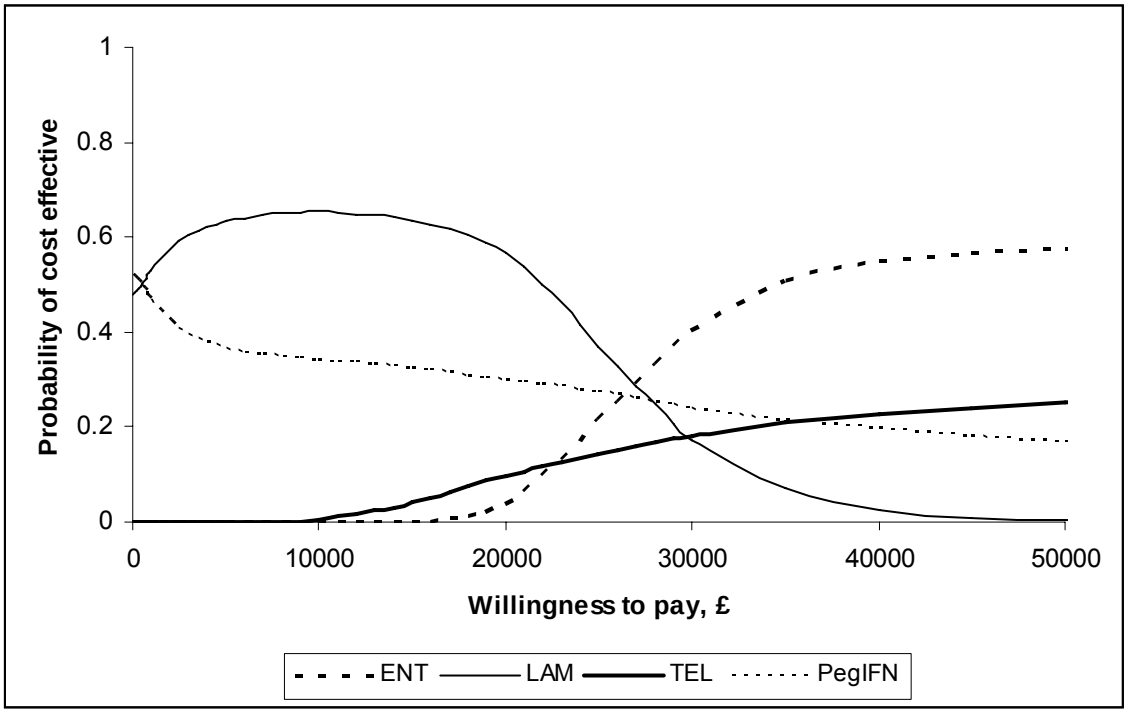
The results for the PSA in the MS show that entecavir has a probability of the ICER being below £20,000 of 57% versus lamivudine; 82% versus pegylated interferon alpha 2a; and 45% versus telbivudine in HBeAg positive patients (MS Table 6.16). For HBeAg negative patients the probabilities were 90%, 100% and 96% respectively (MS Table 6.18). The ERG ran the PSA in HBeAg positive lamivudine refractory patients. The results indicate that a probability of the ICER of entecavir versus combination treatment of lamivudine with adefovir being below £20,000 of 66%.

4.4.1.5 ERG probabilistic sensitivity analysis

The ERG conducted a probabilistic sensitivity analysis using wider uncertainty around the utilities (+/-10%) and drug costs (+/- 20%) than presented in the MS. As noted above, in the HBeAg positive model, patients with CHB were treated for two years with entecavir, lamivudine or telbivudine but, it was considered more appropriate for them to be treated for longer. The ERG attempted to run the HBeAg positive model for a longer duration but the results were inconsistent with those from the deterministic scenario analyses.

The ERG ran the HBeAg negative model for a lifetime treatment duration. The model was amended so that patients with compensated cirrhosis would also receive treatment, lasting until they develop decompensated cirrhosis, HCC or die. As can be seen from Figure 3, according to the manufacturer's model, the probability of entecavir being cost effective at a willingness to pay of £20,000 and £30,000 is 4% and 40% respectively.

Figure 3 - Cost effectiveness acceptability curve for entecavir, lamivudine, telbivudine and pegylated interferon for the HBeAg negative model



ENT= entecavir; LAM = lamivudine; TEL = telbivudine, PEG IFN = pegylated interferon alpha

4.4.2 Comment on validity of results presented with reference to methodology used

In general, the approach to the modelling is reasonable. However, the concerns are raised in relation to:

- The uncertain effect of the modelling assumption of patients with response transitioning exclusively to the inactive cirrhosis state;
- The appropriateness of including the "flare due to resistance state" given the uncertain direction of transitioning between flares and resistance (i.e. what comes first) and the cycle length of one year;
- The durations of nucleoside treatment in the base case analyses of two and five years in HBeAg positive and HBeAg negative patients respectively, which do not correspond to clinical practice (where patients who do not achieve a response continue to receive treatment for life);
- The exclusion of patients who progress to the active cirrhosis state from receiving treatment for CHB;
- The assumption that all the patients are first presented at the pre-cirrhotic state of disease;
- The uncertainty in relation to the validity and reliability of some transition probabilities used in the model (e.g. probability of achieving a response in year two).
- Applicability of estimates of differential probabilities of transitioning to the active cirrhosis state in HBeAg positive patients who did not achieve seroconversion but nevertheless responded to treatment in terms of viral load suppression. The probability calculations rely on the relationship between the viral load and the risk of cirrhosis elicited from a single prospective, population-based cohort study of untreated Taiwanese individuals. It is uncertain whether the probability estimates obtained from the observational study and from the various studies of uncertain methodological quality (Lau *et al*, 2005[28], Han *et al*, 2007[31], Lai *et al*, 2005[27]) are (a) valid and (b) applicable to the UK population.
- The applicability of utility weights elicited from 100 uninfected UK residents to the entire population of CHB patients; also the unexplained discrepancy in utility values assigned to the patients in the compensated cirrhosis state, liver transplant and post-liver transplant health states in the MS model and the model reported in Shepherd *et al*, (2006)[7].

Given these concerns the ERG would suggest that the modelled economic evaluation might have produced an overestimate of the cost-effectiveness of entecavir in HBeAg positive and

HBeAg negative patients. The ERG agrees with the concerns raised by the manufacturer in relation to the cost effectiveness of entecavir in treatment of lamivudine-resistant patients.

4.4.3 Summary of uncertainties and issues

- The duration of treatment assumed in the models is poorly justified. The ERG clinical experts felt that for the majority of patients the treatment lasts longer than the two and five years assumed in the HBeAg positive and HBeAg negative disease models. The MS provided the lifetime treatment scenario for the HBeAg negative disease which the ERG clinical experts felt is the most appropriate model. However, there is an uncertainty associated with the paucity of clinical effectiveness data beyond the second year of treatment.
- Methods of deriving the year two estimates of response to treatment (footnotes to MS Tables 6.4 and 6.5) are not clear but appear to be based on the assumption of drop out rates being the same across all treatment groups. This assumption does not seem to be reasonable. The resulting estimates of response rates used in the model may bias the cost-effectiveness results in favour of entecavir.
- The model assumption about the clinical practice of excluding patients who progress to the active cirrhosis state from receiving further treatment for CHB is not supported by the ERG clinical expert. As demonstrated by the ERG scenario and PSA analysis, this assumption significantly biases the estimated ICER(s) in favour of entecavir.
- The assumption that all the patients are first presented at the pre-cirrhotic state of disease is not supported by the ERG clinical expert. As demonstrated by the ERG scenario and PSA analysis, this assumption significantly biases the estimated ICER(s) in favour of entecavir.

5 Discussion

5.1 Summary of clinical effectiveness issues

- The evidence for the efficacy and safety of entecavir compared to lamivudine presented by the manufacturer comprises five published RCTs, which the ERG consider to be generally sound based on critical appraisal. The results of the individual trials show that entecavir is statistically superior across most outcomes. However, randomised data are only available for one year of treatment. Observational open-label follow-on studies are in progress which will report on the outcomes of treatment up to five years.

- There is a lack of head-to-head data for entecavir versus other comparators in both nucleoside naïve and lamivudine-refractory patients. The MTC model constructed by the manufacturer for nucleoside naïve patients permits both direct and indirect comparison of the drugs, but suffers from a number of weaknesses, particularly the lack of trials for some of the drugs in some of the patient sub-groups.
- None of the RCTs reported the impact of entecavir on health related quality of life. Consequently the manufacturer's submission lacks direct evidence on this important outcome.

5.2 Summary of cost effectiveness issues

The conceptual structure of the MS model appears reasonable and is generally in accordance with the decision problem and the NICE reference case. However, the ERG is primarily concerned about the following assumptions in the model that do not appear to correspond to clinical practice and are likely to have introduced a significant bias in the cost-effectiveness analysis in favour of entecavir:

- The duration of nucleoside treatment in the base case analyses of two and five years in HBeAg positive and HBeAg negative patients respectively, which does not correspond to clinical practice where patients who do not achieve a response continue to receive treatment for life;
- The exclusion of patients who progress to the active cirrhosis state from receiving further treatment for CHB is not explained in the MS and does not reflect clinical practice;
- The assumption that all the patients are first presented at the pre-cirrhotic state of disease is not discussed in the MS and does not reflect clinical practice.

6 Appendices

Appendix 1: Manufacturer's response to clarification queries

Bristol-Myers Squibb response to clarification questions asked by the Evidence Review Group (ERG), received 24th December 2007

Responses to STA NICE/ERG Clarification letter 12th December 2007	
Approved name of medicinal product:	Entecavir
Brand name:	Baraclude
Company:	Bristol-Myers Squibb Pharmaceuticals Ltd
Submitted by:	Toby Gosden
Position	Associate Director, Outcomes Research
Date:	21st December 2007

Section A: Clarifications of the effectiveness data

Literature searching

A1. It is stated that "no time limits were applied" for the clinical and cost effectiveness search strategies. Please can you specify the inception date of the databases (as this varies according to the host system used).

1) Clinical search strategy:

No date limits were applied to following databases - Inception dates of (where known) are shown:

- ***EMBASE using Dialog Datastar - 1974 to date ('date' = approximately the 21st September 2007)***
- ***MEDLINE using Ovid & Dialog Datastar - 1950 to date ('date' = approximately the 21st September 2007)***
- ***Cochrane Cochrane Systematic Reviews Database – 1800 to 2007 (default)***
- ***Cochrane Central Register of Controlled Trials – 1800 to 2007 (default)***
- ***DARE database – 1995 to present / HTA database – 1988 to present – searched jointly on Centre for Reviews & Dissemination website (www.crd.york.ac.uk)***

Inception dates could not be identified for the following databases (no date limits were specified in search):

- ***PreMedline using Dialog Datastar***
- ***Clinical trials clinicaltrials.gov website (www.clinicaltrials.gov)***
- ***Current Controlled Trials website (www.controlled-trials.com)***

2) Cost effectiveness search strategies:

No date limits were applied to following databases – Inception dates (where known) are shown:

- ***MEDLINE - 1950 to Sept 2007 / MEDLINE (R) In-Process (inception date not applicable) – searched jointly on pubmed (www.ukpmc.ac.uk)***
- ***EMBASE (1974 to present) /MEDLINE (1966 to present) - searched jointly on Embase website (www.embase.com)***
- ***DARE – 1995 to present; NHS EED – 1995 to present; HTA – 1988 to present – searched jointly on Centre for Reviews & Dissemination website (www.crd.york.ac.uk/)***
- ***Cochrane databases (see Cochrane Library - www.mrd.interscience.wiley.com/cochrane/) – default used of 1800 to 2007***

Inception dates could not be identified for the following databases (no date limits were specified in search):

- ***TRIP (www.tripdatabase.com)***

A2. Please could you specify which host system was used for the clinical effectiveness searches? It appears that the replication of the SHTAC search strategy (referred to as search #1 in Appendix 8.2, sub-section 8.2.4) was conducted using Ovid Medline. However the host system for searches #2 and #3 are not mentioned.

Host systems used for search strategy #2:

- ***Dialog Datastar (Embase)***
- ***Ovid & Dialog Datastar (Medline)***

Host systems used for search strategy #3:

- ***Ovid & Dialog Datastar (Medline)***
- ***Dialog Datastar (PreMedline; Embase)***
- ***Cochrane Library (www.mrd.interscience.wiley.com/cochrane/) for Cochrane Systematic Reviews Database & Cochrane Central Register of Controlled Trials***
- ***NHS CRD database website (www.crd.york.ac.uk) for DARE; Health Technology Assessment (HTA) database***
- ***Clinical trials.gov website (www.clinicaltrials.gov)***
- ***Current Controlled Trials website (www.controlled-trials.com)***

A3. Please could you provide the clinical effectiveness search strategies as tailored for each of the databases listed (e.g. Embase, Cochrane etc), together with the number of hits generated by each database. It would be useful to see how the strategy has been tailored for each database (and the results) so that it can be reproduced if necessary.

The results of the individual search strategies for each database were not saved by the agency commissioned to undertake the systematic review, therefore, these cannot be provided. The appendix at the end of this document does, however, provide the search strategies used for Embase, Medline (Dialog Datastar & Ovid) and the Cochrane Library databases. For the other databases (CRD databases, www.clinicaltrials.gov,

www.controlled-trials.com), each generic drug name combined with 'hepatitis B' was used in the search strategy.

A4. Search line 10 in the strategy #2 (Appendix 8.2) – at the end of the line is 'tnwas'. Please can you confirm whether this is recognised syntax or whether it is a typo (in earlier lines of the strategy 'tn' is used).

This is a typographical error. It should read: 10. (("polyethylene" and "glycol*") or "peg*"):ti,tt,ab,tn. To confirm, 'tn' was used in the search strategy rather than 'tnwas'.

A5. Search line 20 in the strategy #2 (Appendix 8.2) is recorded as '16 OR 17 OR lit OR 19'. We are unclear what 'lit' refers to and wonder whether it is a typo for '18'. If the latter please can you indicate what difference this makes to the search results.

'lit' was not used in the original search strategy. '18' was used instead. Hence this is a typographical error.

A6. Please can a list of the excluded studies be provided for each drug, with the reason for exclusion for each one (if possible).

A tabulation of the number of studies excluded by reason is provided in Appendix 8.3.2 of the submission. However, within the timeframe given to respond on these issues of clarification, it is not feasible to attribute the reason for exclusion to each study excluded.

Individual RCTs

A7. Tables 5.5, 5.6, and 5.7 list the proportion of patients attaining an HBV DNA of <300 copies/ML by PCR as well as the proportion attaining an HBV DNA of <0.7 ME/q/ML by branched DNA. These evaluations use different assays, but we are unclear as to how comparable they are in terms of a patient's viral load. Given that the proportions vary quite considerably between these two assays we would be grateful if you could clarify.

HBV DNA < 0.7 MEq/mL by bDNA is equivalent to 700,000 copies/mL.

A8. Table 5.1 (page 36) lists 12 RCTs of entecavir, yet the QUOROM flow chart (Fig 5.2.6, page 42) and Appendix 8.3.2 both list 10 papers. Please can you explain this discrepancy.

In addition to the 10 studies identified as relevant in the systematic review, two further studies were also identified from BMS internal records. The QUOROM flow chart (Fig 5.2.6, page 42) and Appendix 8.3.2 include only studies from the clinical systematic review. Table 5.1 includes the additional studies found from the search of BMS records.

A9. Table 5.5 (p.69) lists a complete virological response as 'HBV DNA and <0/7 MEq/ml by bDNA and ALT<1.25xULN'. However, on page 44 in the table a 'complete virological response' is defined as undetectable HBV DNA by bDNA assay and undetectable HBeAg. The figures presented in Table 5.5 correspond with those reported on page 1006 in the journal publication for this trial (Chang *et al*), which defines complete virological response as 'HBV DNA by bDNA assay and undetectable HBeAg'. Please can you clarify whether or not this is a typographical error.

This is a typographical error. In table 5.5 Complete virological response should be defined as undetectable HBV DNA by bDNA assay and undetectable HBeAg.

A10. Statistical significance not reported in Table 5.5 (p.69), 5.6 (p73) for the proportion of complete virological responders / partial responders / non-responders. We presume this is because these were not efficacy outcome measures per se, but governed whether or not patients proceeded to year 2 of treatment. Please could you clarify.

For the studies included in Tables 5.5 and 5.6 (studies 022 & 027), treatment comparisons (with statistical significance) at week 48 were conducted for complete virological responders, but not for partial responders or non-responders.

Throughout the submission publications were used as the primary data source for each study. Hence for study 022 (Table 5.5, page 69) statistical significance for complete virological responders at Week 48 was not reported in the table, as it was not available in the primary publication (Chang et al). Please find below the p value as reported in the CSR for this study (reference 57):

Endpoint	Entecavir 0.5mg N=354	Lamivudine 100mg N=355	Difference Entecavir-lamivudine (95% CI)	P-Value
Complete virological responders: HBV DNA <0.7 MEq/mL by bDNA and HBeAg negative, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Note: Commercial in confidence information is highlighted in above table

For Study 027 (Table 5.6, page 73) statistical significance for complete virological responders at Week 48 was reported in both the publication (Lai et al. (reference 58) and the CSR (reference 59) and is included in Table 5.6 (p73).

A11. Statistical significance is not reported for the year 2 cohort and 24 week post treatment follow-up for complete virological responders, as presented in Tables 5.5, 5.6, 5.7, and 5.8. Please can clarify why this was not presented, and supply the results if available.

According to the relevant clinical study reports, statistical comparisons for the year 2 cohort and 24 week post treatment follow-up for complete virological responders were not planned or undertaken for studies 022, 026, 027 and 023.

A12. Table 5.6 (p.73) states that patients were both HBeAg-ve and +ve in study 027, yet elsewhere this study is described as HBeAg-ve patients only. We presume this is a typographical error, please clarify.

To confirm that this is a typographical error, patients in study 027 were HBeAg-ve only.

A13. Table 5.9 the numbers for the patients in the entecavir and lamivudine groups should be 42 and 45 respectively as per Table 5.3.2, and not 141 and 145 respectively – we presume this is a typographical error carried over from table 5.8, please clarify

To confirm that this is a typographical error, the number of patients in the entecavir and lamivudine groups should be 42 and 45 respectively.

A14. Page 80 – we presume that in the table reporting secondary outcomes that the dose of entecavir should be 1.0mg not 0.5mg, as per table 5.3.2, please clarify

To confirm that this is a typographical error, the dose of entecavir should be 1.0mg not 0.5mg.

A15. Pages 75 and 76 – the total number of HBeAg positive patients in the study by Yao *et al* is reported as 255. However, for the percentages of patients responding on the various outcomes to make sense this needs to be 225, as is reported on page 74. Please can you clarify.

To confirm that this is a typographical error, the total number of HBeAg positive patients in the study by Yao et al is 225.

A16. Appendix 8.3, table at top of page 3. Under 'Final number for further review' there are 14 reports listed for entecavir – yet in the table on page 6 it says 18. Please clarify this discrepancy.

14 reports is an error. It should be 18 reports for both Appendix 8.3, table at top of page 3 and page 6.

Mixed treatment comparison

A17. Appendix 8.4 (mixed treatment comparison) – please could you clarify the role of adefovir in the analysis. Adefovir is not included as a comparator in the analyses for the naïve patient group, therefore is it included as a means of connecting entecavir with telbivudine? Also, the description of the model does not refer to any particular common comparator (although lamivudine appears to be common to most comparisons). Please can you clarify whether the analysis was designed around a common comparator.

In addition to using trial comparisons with lamivudine to connect entecavir with telbivudine, adefovir was used in the mixed treatment comparison to strengthen this connection. The analysis was based on a network of evidence and was not restricted to a common comparator for all interventions. For example, if there were four interventions A, B, C and D and information for A vs. B, B vs. C and C vs. D then it is possible to get information on A vs. D even though there is no common comparator between A and D. The analysis did use entecavir as the baseline against which all log odds were calculated but this does not mean that it is a common comparator.

A18. Appendix 8.4 (mixed treatment comparison) – Page 17 on the right hand side of the figure labelled 'HBeAg seroconversion' the study by Lai *et al* 2005a – doesn't appear to be connected to anything (the trial compares lamivudine with telbivudine), please can you clarify why.

Lai et al 2005a was a phase 2, dose escalation study comparing various doses of telbivudine to lamivudine given at the recommended dose. The study did not separate out results by dose for all endpoints and hence it was not possible to extract the relevant information. This meant that for some endpoints (e.g. HBeAg seroconversion) there was only information for one arm.

A19. Appendix 8.4 (mixed treatment comparison) it is stated that there were "110 studies identified as part of the review of clinical effectiveness". However, according to the figures presented in Appendix 8.3 we calculated that the number should be 109 (63 lamivudine; 15 pegylated interferon; 19 adefovir; 10 entecavir; 2 telbivudine). We presume this is a typographical; error, please clarify.

This is a typographical error. The 109 studies identified during the systematic review of clinical effectiveness were scanned for information relevant to the network meta-analysis.

A20. In Appendix 8.4 (mixed treatment comparison) on page 2 it reports that 19 published studies met the criteria for the MTC and a further 5 clinical study reports contained useful information. "Therefore 24 studies were included…". However, this figure may be incorrect. Three of the study reports appear to duplicate some of the 19 published studies:
a. Reference 4 – is the CSR for Study 022 which appears to relate to Reference 12 (Chang *et al* 2006)
b. Reference 6 is the CSR for Study 026 which appears to relate to Reference 25 (Sherman *et al* 2006)
c. Reference 7 is the CSR for Study 027 which appears to relate to Reference 18 (Lai *et al* 2006).
d. Therefore it would be more accurate to state that there were 24 reports describing a total of 21 studies. At present there appears to be double counting which erroneously inflates the number of actual studies in the MTC. Please can you clarify whether our calculations are correct.

It is correct that there were 24 reports describing a total of 21 studies. For each of the three studies listed above, the publications were used as the source for 1 year efficacy data, and the clinical study reports were used for all year 2 data.

A21. Were the studies included in the MTC assessed for their methodological quality?

Only randomised controlled trials were included in the MTC but a complete assessment of the methodological quality of each of these trials was not undertaken.

A22. Were any attempts made to estimate heterogeneity and if so what were the results?

There were insufficient data to allow a reliable estimate of a random effects variance to be obtained.

Section B: Economic Analysis

B1. Both models (i.e. for HBeAg+ve and HBeAg-ve sub-groups of patients) include a health state labelled "Flare d/t resistance" which is associated with an elevated risk of decompensated cirrhosis and liver transplant.

a. Please provide the source of clinical evidence (a publication and the page number with relevant estimates) for calculating the "Difference in flare rate between resistant and non-resistant patients".

Lok et al, Gastroenterology 2003;125: 1714-1722. Please see p. 1719, Table 4, row labelled 'ALT >10 x ULN'.

b. Please clarify the meaning of "Flare d/t resistance" health state, in particular, the statement "This is the *attributable* risk of severe flare due to resistance from Lok LMV safety summary" ('Inputs!' B153).

Flare due to (d/t) resistance is the annual incidence of severe flares (defined as ALT >10x ULN) for patients who develop resistance. In Table 4 of Lok et al 2003, the average rate of severe flare for patients with resistance across 5 years is approximately 2-3% per year.

c. Please clarify the clinical justifications of transition probabilities from the "Flare d/t resistance" health state to other states (Response, CHB Resist Salvage Tx, CHB no TX, etc.). In particular, please explain the clinical rationale of a transition probability from "Flare d/t resistance" to SC (seroconversion state) in the HBeAg+ve model. This non-zero probability does not correspond to Figure 6.3 (p.110) that has no transition between these 2 states depicted.

We did not identify any data on the probability of seroconversion ('Response') in patients who had experienced a severe flare due to resistance, and thus assumed they had a seroconversion rate the same as baseline, untreated patients.

The Flare health state is a tunnel state to reflect the clinical nature of a severe flare, which is a more acute event. Patients in the Flare state either develop complications (e.g. HCC, decompensation, liver transplant) or do not. Those patients that do not have a complication related to the flare, are likely to remain resistant and be on salvage therapy. In the model, this last group of patients move from the Flare state to the 'CHB Resist Salvage Tx' state.

The risks of complications (decompensation and liver transplant) from the Flare health state were estimated from Lok et al 2003 and Yuen et al 2003. Lok reported that roughly 5-20% of patients with ALT> 10xULN decompensated; Yuen et al in a study of 18 patients with LMV resistance and severe flares reported that 3 patients decompensated, 1 of whom required a liver transplantation and 1 of whom died.

Patients only move from the Flare state to the CHB no treatment (CHB no tx) state when treatment is stopped, which in the base case is 2 years for HBeAg+ve patients and 5 years for HBeAg-ve patients.

d. Please provide the rationale for a 9% transition probability from "Flare d/t resistance" to SC (seroconversion state), which is "Set Equal to CHB rate" ('Inputs!' H209).

Please see response above.

e. Also, please provide the clinical rationale for assigning transition probabilities from CHB to the "Flare d/t resistance" health state only to entecavir and interferon treatment in the HBeAg+ve model and only to entecavir and lamivudine treatment in the HBeAg-ve model.

All patients who experienced resistance should have a risk of severe flare (2% absolute risk). Interventions without resistance (at all, or in earlier years) will not have patients transitioning from CHB to 'Flare due to resistance'. Since there is no resistance in peginterferon use this is necessarily 0. Similarly, in the positive model when treatment is not being given the probability is necessarily 0. For all other occasions, for all drugs in both models, there is a (very small) probability derived.

Note that in the transition matrix sheets, only patients who are being treated (CHBtx) can experience flares; untreated patients (CHB) cannot.

B2. Both models include an "Inactive (non-replicating) cirrhosis" health state along with "Active (compensated) cirrhosis" state in both the HBeAg+ve and HBeAg-ve models. It appears from the HBeAg-ve model structure presented in the EXCEL spreadsheet that patients in "Response", "Response with resistance" and "Response to salvage Tx" health states can only enter the "Active cirrhosis" state via an "Inactive cirrhosis" state. The underlying clinical rationale for such structure of the model does not seem to be provided. The submission emphasises the importance of the [differential] risk of cirrhosis, however in the context of the clinical evidence (section 6.2.8) no distinction is made between inactive (non-replicating) cirrhosis and active (compensated) cirrhosis. Please provide clinical justification of the suggested disease progression pathway and explain the different roles of the "Inactive cirrhosis" and "Active cirrhosis" health states in the models.

In the HBeAg-ve model, patients who have achieved Response cannot progress directly to active cirrhosis. This is analogous to patients in the HBeAg+ve model who have achieved HBeAg seroconversion. These transitions were not allowed for consistency with the course of disease – patients with inactive disease are not likely to become cirrhotic with inflammatory response without first seroreverting or becoming HBV DNA positive.

The 'Inactive cirrhosis' health state was included to account for finer details of the disease that the clinicians we spoke to felt might be important to include in the model, although this state has relatively little impact on the results of the analyses. For example, the transition probability from response/seroconversion to the inactive cirrhosis state is 0.1%; increasing this estimate by even 10-fold has little effect. The estimate of progression from HBeAg-seroconversion to inactive cirrhosis was derived from Hsu et al, who described 189 patients that seroconverted and remained persistently HBeAg-negative with normal ALT over a 9-year follow-up. Of those, only 1 patient developed

cirrhosis during a median of 99 months of follow-up, which corresponded with an annualized incidence of cirrhosis of less than 0.1%.

B3. Was the clinical evidence used to obtain the estimate of a significantly lower risk of developing a decompensated cirrhosis (0.8%) (Fattovich *et al*, 2002, Table 6.3, p.113) observed in the population that is identical to the cohort of patients in the model (i.e. patients with "inactive cirrhosis")? Also, please provide a clinical rationale for assigning the value of transition probability from compensated cirrhosis to inactive cirrhosis as being equal to the probability of spontaneous response from the CHB state.

The patients in Fattovich et al. (2002) had compensated cirrhosis, which could be either active (HBV-DNA positive) or inactive (HBV-DNA negative), whereas in the model, the transition probability (inactive cirrhosis to DCC) refers to patients with inactive cirrhosis only. Rates of decompensation were not reported separately for active and inactive cirrhotic patients in Fattovich et al. but the study found that the risk of hepatic decompensation in patients with positive HBV-DNA (active cirrhosis) compared with patients with negative HBV-DNA (inactive cirrhosis) was approximately 4 fold higher (see Table 5, p. 2891). The annualised rate of decompensation of 3.1% in patients with both active and inactive cirrhosis (calculated from the percentage of HBsAg positive patients (20%) developing decompensation over a median of 77 months – see Table 2 p2889) was divided by 4 to obtain the 0.8% value for the inactive cirrhosis patients.

HBeAg-positive patients who have developed cirrhosis may still seroconvert and go into a non-replicative phase of disease (Liaw et al, Liver, 1989; 9(4):235-41). We did not have specific data on the probability of transitioning from active to inactive disease, and thus assumed this occurred at the same rate as that of baseline seroconversion (or probability of moving from CHB tx to Response). Changing the probability of transitioning from active to inactive cirrhosis has only a small impact on the incremental results – for instance, changing it from 9% to 0% changes the ICER in the entecavir vs. lamivudine comparison from £8,403 to £7,226 in the HBeAg positive model.

B4. What were the dose regimens and duration of therapy used in the scenario analysis of ENT monotherapy vs the combination of lamivudine and adefovir in treatment naïve patients? (p.140). Please provide the values of the estimates of clinical effectiveness of the ENT monotherapy vs LVD/ADV used in the scenario analysis.

For the comparison of ENT monotherapy vs LDV/ADV, the dose and duration of therapy for ENT were the same as that used in comparisons of ENT monotherapy with alternative monotherapies in HBeAg positive treatment naïve patients i.e. 0.5mg once daily for 2 years. The ADV/LDV combination uses the standard dosing regimens for lamivudine (100mg once daily) and adefovir (10mg once daily) combined.

In terms of clinical effectiveness, the seroconversion rates for years 1 and 2 for entecavir of 18.3% and 10.4% were taken from the network meta-analysis. The effectiveness of adefovir/lamivudine was taken from Marcellin et al. 2003, and rates of seroconversion of 12% in year 1 and 15.7% in year 2 were used. Rates of resistance for entecavir were taken

from the summary of product characteristics, and in the absence of specific resistance data for ADV/LVD in a naïve population, resistance was assumed to be the same as ADV monotherapy i.e. 0%.

Appendix

Embase search strategy

No.	Search term
1	hepatitis ADJ b OR hepatitis ADJ b ADJ chronic
2	hepatitis ADJ b ADJ virus OR hepatitis ADJ b ADJ antibodies
3	hbv OR hepatitis-b OR HBeag ADJ negative OR hbeag ADJ positive OR hbsag
4	1 OR 2 OR 3
5	pegylat$ ADJ interferon$ OR peg-ifn OR peginterferon$ OR pegasys OR pegintron OR viraferonpeg
6	interferon ADJ alpha ADJ 2a OR interfron ADJ alfa ADJ 2a OR interferon ADJ alpha ADJ 2b OR interferon ADJ alfa ADJ 2b OR alpha ADJ interferon OR intron OR viraferon OR roferon OR interferon-alpha OR interferon-alfa
7	interferon-alpha OR interferon-alfa
8	6 OR 7
9	polyethylene ADJ glycols
10	polyethylene AND glycol$ OR peg$
11	9 OR 10
12	8 AND 11
13	5 OR 12
14	13 AND 4
15	14 AND LG=EN
16	adefovir ADJ dipivoxil OR adefovir$ OR hepsera
17	telbivudine
18	lamivudine
19	entecavir
21	16 OR 17 OR 18 OR 19
22	21 AND 14
23	LG=EN
24	AT=ARTICLE OR AT=REVIEW OR AT=SHORT-SURVEY
25	22 AND 23 AND 24
26	22

Medline Search Strategy

#	Search History
1	(((hepatitis adj b) or hepatitis) adj b adj chronic).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
2	(((hepatitis adj b adj virus) or hepatitis) adj b adj antibodies).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3	(((((hbv or hepatitis-b or HBeag) adj negative) or hbeag) adj positive) or hbsag).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4	1 or 2 or 3
5	((pegylat$ adj interferon$) or peg-ifn or peginterferon$ or pegasys or pegintron or viraferonpeg).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6	((((((((((interferon adj alpha adj 2a) or interferon) adj alfa adj 2a) or interferon) adj alpha adj 2b) or interferon) adj alfa adj 2b) or alpha) adj interfron) or intron or viraferon or roferon or interferon-alpha or interferon-alfa).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
7	(interferon-alpha or interferon-alfa).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
8	6 or 7
9	(polyethylene adj glycols).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10	((polyethylene and glycol$) or peg$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
11	9 or 10
12	8 and 11
13	5 or 12
14	13 and 4
15	limit 14 to english language
16	((adefovir adj dipivoxil) or adefovir$ or hepsera).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
17	telbivudine.mp.
18	lamivudine.mp. or Lamivudine/
19	entecavir.mp.
20	16 or 17 or 18 or 19
21	20 or 15
22	limit 21 to (clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or journal article or meta analysis or multicenter study or randomized controlled trial or "review")

Cochrane search strategy (for entecavir as an example)

1	“hepatitis b” AND entecavir
2	#1 and Cochrane Reviews

*these referred to five protocols (table below) – **not sure table below is necessary**

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